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PATENT SPECIFICATION

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(19)

(72) Inventors GUNTER SCHMIDT and KARL GEORG METZGER

(54) NEW PENICILLINS, THEIR PRODUCTION AND THEIR PHARMACEUTICAL USE

(71) We, BAYER AKTIENGESELLSCHAFT, a body corporate organised under the laws of Germany, of Leverkusen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to certain new penicillin compounds, to their production, and to their use in human and veterinary medicine, especially for treating bacterial infections of acute and chronic nature, as well as for feedstuff additives and growth-promoting agents for poultry, mammals and fish.

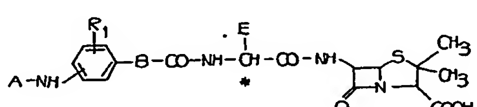
It has already been disclosed that substituted 6-(α-benzoylamino)-acetamido-penicillanic acids which in the 3- or 4-position of the benzoyl radical carry a substituent derived from carbonic acid, of the general formula:—

$$R—X—\overset{\overset{\displaystyle O}{\|}}{C}—X—$$

[in which X represents O or NH] can be synthesised; they are described in German Offenlegungsschrift No. 2,050,087.

On the other hand, those penicillin derivatives in which the amino groups in the *ortho-*, *meta-* or *para-*position of the benzoyl radical are not substituted by carbonic acid derivatives have not previously been disclosed.

This invention now provides new compounds which are penicillins of the following general formula and their salts:—



(I)

in which

R_1 is a hydrogen, halogen, lower alkyl, hydroxyl, A—NH— or nitro radical;

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A is a radical R_2 or

$$R_3-\overset{\displaystyle O}{\overset{\|}{C}}- \text{ or } R_4-\overset{\displaystyle S}{\overset{\|}{C}}-$$

[in which:—

R_2 is a hydrogen, lower alkyl or arylsulphenyl radical;

R_3 is a hydrogen, lower alkyl, halo-(lower alkyl), cycloalkyl or cycloalkenyl radical with up to 11 carbon atoms; a bicycloalkyl or bicycloalkenyl radical with up to 8 carbon atoms, an aryl radical carrying at least one substituent, or an azidoaryl, azidoalkyl, amino, cinnamoyl, *p*-aminophenyl or heterocyclyl radical;

R_4 is a lower alkylamino, arylamino or (substituted aryl)-amino radical];

B is a single bond or a group $-CH_2-$, $-S-CH_2-$, $-CH=CH-$ or $-CO-NH-CH_2-$;

E is a phenyl radical or a hydroxy-, azido-, lower alkyl-, lower alkoxy-, lower alkylthio- or chlorine-substituted phenyl or thenyl radical; and

C^* is an asymmetric carbon atom.

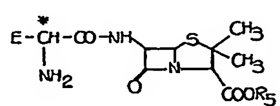
The asymmetric carbon atom C^* gives rise to pairs of R— and S— diastereomers. The invention covers compounds of both diastereomeric configurations both individually and in mixtures.

Throughout this specification the term "compounds of the invention" includes both the free penicillins of general formula I and their salts. Of these salts, those that are pharmaceutically acceptable are preferred.

Such non-toxic, pharmaceutically acceptable salts include especially salts of the acid carboxyl group, such as the simple salts with sodium, potassium, magnesium, calcium, aluminium and ammonia, and the non-toxic substituted-ammonium salts with amines, such as di- and tri-lower alkyl-amines, procaine, dibenzylamine, N,N'-dibenzylethylenediamine, N-benzyl-β-phenylethylamine, N-methyl- and N-ethyl-morpholine, 1-ephenamine, dehydroabietylamine, N,N'-bis-dehydroabietylethylenediamine, N-lower alkylpiperidine and other amines which have already been used for forming salts of penicillins.

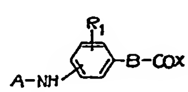
The terms "lower alkyl" and "lower alkoxy" are to be understood, in the present specification, as meaning straight-chain or branched alkyl or alkoxy groups with up to 6 carbon atoms.

This invention further provides a process for the production of a compound of the invention in which an ampicillin derivative of the general formula



(II)

is reacted with a compound of the general formula



(III)

[in which general formulae:—

R_1, A, B and E are as defined above;

R_5 is a hydrogen, trimethylammonium or sodium atom or molecule; and

X is a labile radical

at a temperature of $-20°$ to $+50°C$, in a diluent and in the presence of a base.

The labile radical X can be any radical that is smoothly eliminated as HX together with a hydrogen atom of the free amino group of the ampicillin derivative of general formula II to produce the desired peptide bond. Many such radicals X are known for this purpose from peptide chemistry, the most important for the purposes of the present invention being the halogens (especially chlorine), acyloxy groups (especially acetyl) and activated ester groups (especially benzotriazol-ethoxycarbonyl-oxy-1-yl).

The synthesis of the activated acylated aromatic amino acid of general formula III can be carried out by any suitable method; several such methods are known in peptide chemistry, the principal examples for present purposes being the acid chloride method, the mixed anhydride method, and the activated ester method. In general the acylated aromatic amino acid of general formula III (X=OH) is reacted at the carboxyl group in an anhydrous organic solvent and in the presence of about 1 mole equivalent of a tertiary organic base, preferably N-methyl-morpholine, at -60 to $+30$°C, preferably -20 to $+10$°C.; the activated acylated aromatic amino carboxylic acid III (X= labile radical) is preferably not isolated, but reacted immediately with a solution of the ampicillin derivative of general formula II. [see T. Wieland & H. Bernhard, Liebig's Ann. Chem. *572,* 190 (1951); R. A. Boissonas, Helv. Chim. Acta. *34,* 814 (1951); J. R. Vaughan & R. L. Osato, J. Amer. Chem. Soc. *73,* 3,547 (1952)].

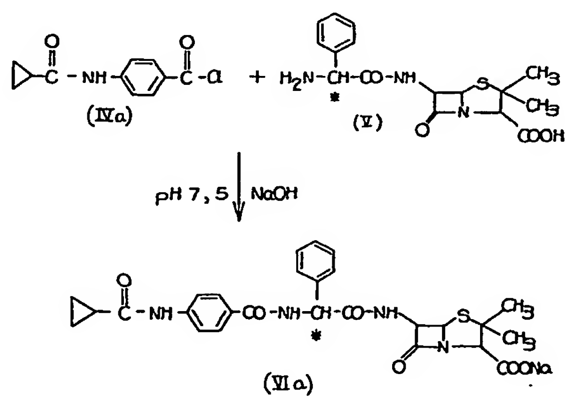
In the acid chloride method, the acylated aromatic amino acid III (X=OH) is generally reacted with thionyl chloride or phosphorus pentachloride in an anhydrous inert organic solvent (e.g. methylene chloride, benzene, tetrahydrofuran (T.H.F.), acetone, dioxane and chloroform) to produce, as the activated acylated aromatic amino acid III (X=Cl) the acid chloride.

In the mixed anhydrides method the acylated aromatic amino acid of general formula III (X=OH) is converted into a mixed anhydride with another carboxylic acid; the residue (X) of the other carboxyl acid is smoothly eliminated in the subsequent reaction with the ampicillin derivative of general formula II. In the most useful form of this method, the acylated aromatic amino acid III (X=OH) is reacted with an alkyl acid chlorocarbonate (preferably ethyl chlorocarbonate) in an inert solvent (e.g. tetrahydrofuran); the acid is preferably first converted to its triethylamine salt. The product is an activated acylated aromatic amino carboxylic acid III in which X is an acyloxy group (when ethylchlorocarbonate is used,

$$X = \text{acetyloxy}\text{—O—}\overset{\overset{\large O}{\|}}{C}\text{—OC}_2\text{H}_5).$$

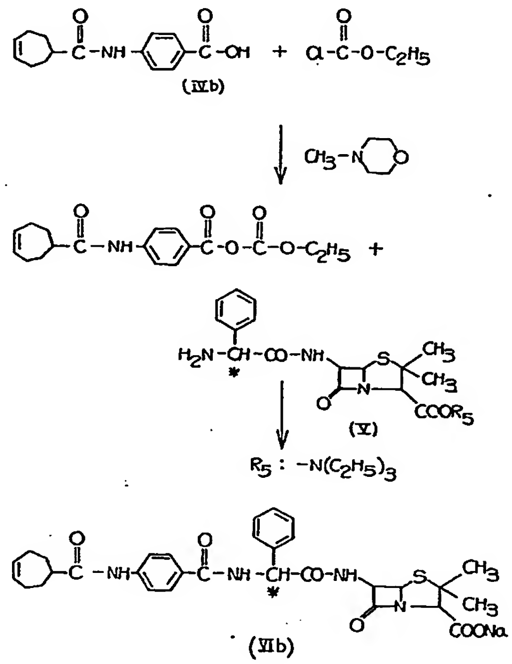
In the activated ester method the acylated aromatic amino acid of general formula III (X=OH) is converted into an ester by reaction with an alcohol the residue (X) of which is smoothly eliminated in the subsequent reaction with the ampicillin derivative II. The most useful activated esters are the 1-hydroxy-benzotriazole ester (W. Konig & R. Geiger, Chem. Ber. *103,* 788—798 [1970]), but other activated esters (e.g. the *p*-nitrophenyl, thiophenyl, cyanomethyl, N-ethyl-5-phenyl-isoxazolium-3′-sulphonate, and N-hydroxyphthalimide esters) can be used. The conditions under which the activated esters are formed are those described above.

If 4-cyclopropanecarbonylamino-benzoyl chloride (IVa) and D-α-amino-benzylpenicillin (= ampicillin) (V) are used as starting compounds, the course of the reaction in the process of the invention can be illustrated by the following equation:



Sodium D-α-(4-cyclopropanecarbonyl-amino-benzoylamino)-benzylpenicillin (VIa) is obtained.

If 4-(4-cycloheptene-1-carbonylamino)-benzoic acid (IVb) and D-α-amino-benzylpenicillin (= ampicillin) (V) are used as starting compounds for a mixed anhydride synthesis, the course of the reaction can be represented by the following equation:

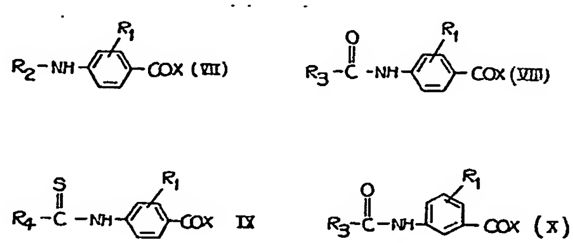


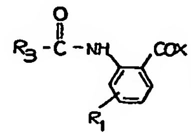
Sodium D-α-[4-(4-cycloheptene-1-carbonylaminobenzoylamino)]-benzylpenicillin (VIb) is obtained.

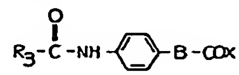
The compounds of the general formula II used as starting materials according to the invention are described in German Patent No. 1,156,078, in U.S. Patents No. 3,342,677, 3,157,600, 2,985,648 and 3,140,282, in South African Patent No. 68/0290 and in U.S. Patent No. 3,144,445. They can occur in the D=R-form or L=S-form depending on the configuration at the centre of asymmetry in the side chain (C*).

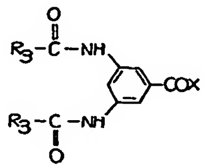
All crystal forms and configurations of the compounds of the general formula II are suitable as the starting material for the reaction according to the invention. The configuration of the centres of asymmetry of the 6-aminopenicillanic acid nucleus in the compound of the general formula II should be identical with the corresponding centres of asymmetry of 6-aminopenicillanic acid which has been obtained, for example, from penicillin G by fermentative processes.

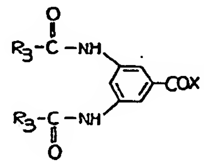
The compounds of the general formula III which can be used as starting compounds according to the invention are in some cases known. The production of typical starting compounds which are not previously known is described in the Examples, and the remainder can be produced analogously. The following are typical examples of starting compounds of the general formula III:



 (XI)

 (XII)

 (XIII)

 (XIV)

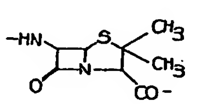
Possible diluents for the reaction of compounds II and III are organic solvents, such as acetone, tetrahydrofuran (THF), dioxane, acetonitrile, dimethylformamide (DMF), dimethylsulphoxide and methylene chloride or mixtures of these solvents with water.

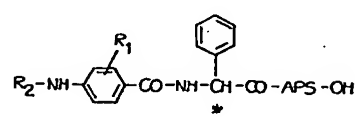
The bases used in the reaction of compounds II and III are generally tertiary organic bases, for example N-methylmorpholine and triethylamine, or inorganic bases. The pH value of the reaction mixture is kept at pH 6.5 to 9.2 with the aid of these bases. Where a pH measurement is not carried out, as in the case of the mixed anhydride technique using absolute organic solvents ($THF/DMF/CH_2Cl_2$), 1.5 to 2.6 mol equivalents of base are preferably added when 6-D-(α-amino-phenylacetamido)-penicillanic acid (ampicillin) and an anhydrous reaction medium are used.

The reaction temperatures can be varied over a substantial range. In general, the reaction is carried out between −20° and +50°C, temperatures of −15° to +20°C being particularly preferred.

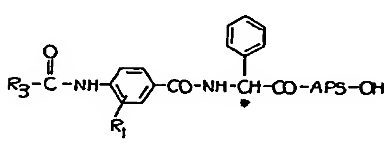
In carrying out the process according to the invention, the reactants of general formulae II and III react with one another in equimolecular amounts. It can, however, be desirable to have one of the two reactants present in excess in order to facilitate the isolation of the desired penicillin and to increase the yields. For example, the reactants of the formula II can be employed in an excess of 10 to 30% per mol, especially when the mixed anhydride or activated ester method is used to produce the compound of general formula III. The excess of the reactant of the general formula II can easily be removed because of its good solubility in aqueous mineral acids when working up the reaction mixture. On the other hand it is also possible advantageously to employ the reactants of the general formula III in an excess of, for example, 10% to 20 mol %, especially when the acid chloride method is used to produce the compound of general formula III. This results in the reactants, for example of the general formula II, being utilised better and compensates for the decomposition of the reactants of the general formulae VII to XIV which takes place as a side-reaction in aqueous solvents.

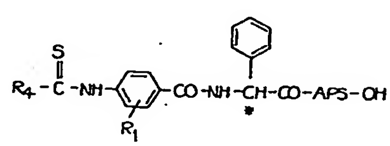
Preferred groups of compounds according to the invention are the penicillins represented in the following general formulae and their salts. Unless otherwise stated, the radicals R_1, R_2, R_3 and R_4 can have any of the meanings given above, and —APS— is the divalent radical:—

 :—

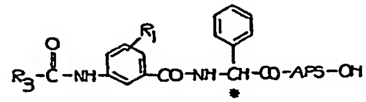


in which R_1 is a hydrogen, nitro or halogen radical;

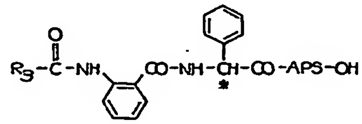
 ;



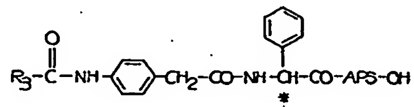
in which R_1 is a hydrogen, nitro or halogen radical;

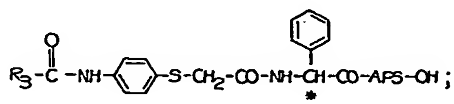


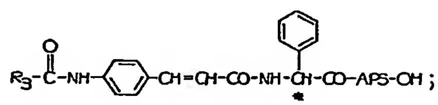
in which R_1 is a hydrogen or halogen radical, and R_3 is a hydrogen or lower alkyl radical or a cycloalkyl or cycloalkenyl radical with up to 11 carbon atoms;

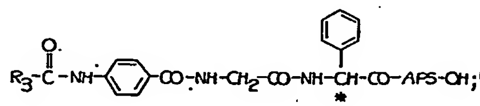


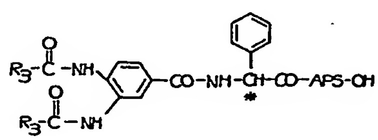
in which R_3 is a hydrogen or lower alkyl radical or a cycloalkyl or cycloalkenyl radical with up to 11 carbon atoms;



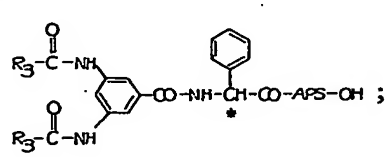








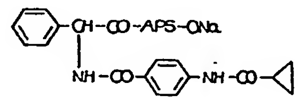
in which R_3 is a hydrogen or lower alkyl radical or a cycloalkyl or cycloalkenyl radical with up to 11 carbon atoms;



in which R_3 is a hydrogen or lower alkyl radical or a cycloalkyl or cycloalkenyl radical with up to 11 carbon atoms.

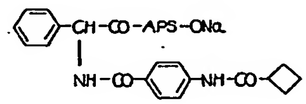
Individually, the following may be mentioned as preferred active compounds according to the invention: ("APS" having the meaning given above):

Sodium D-α-(4-cyclopropanecarbonylamino-benzoylamino)-benzylpenicillin:



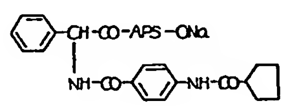
(Example 1)

Sodium D-α-(4-cyclobutanecarbonylamino-benzoylamino)-benzylpenicillin:



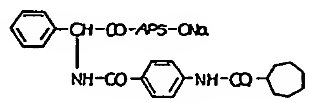
(Example 5)

Sodium D-α-(4-cyclopentanecarbonylamino-benzoylamino)-benzylpenicillin:



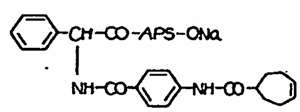
(Example 7)

Sodium D-α-(4-cycloheptanecarbonylamino-benzoylamino)-benzylpenicillin:



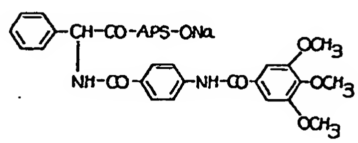
(Example 13)

Sodium D-α-(4-[4-cycloheptene-1-carbonylamino-benzoylamino])-benzylpenicillin:



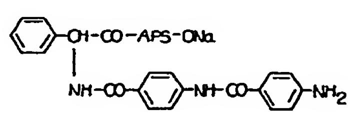
(Example 14)

Sodium D-α-(4[3,4,5-trimethoxybenzoylamino-benzoylamino)]-benzylpenicillin:



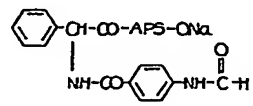
(Example 22)

Sodium D-α-(4-[4-aminobenzoylamino-benzoylamino])-benzylpenicillin:



(Example 29)

Sodium D-α-(4-formylamino-benzoylamino)-benzylpenicillin:



(Example 41)

Surprisingly, most of the new compounds according to the invention display a substantially greater anti-bacterial action against many bacterial strains than the known commercial products ampicillin and carbencillin, and thus represent an enrichment of pharmacy.

Table 1 which follows shows the *in vitro* inhibitory values (MIC) in U/ml of nutrient medium. The determination was carried out in a liquid medium in the test tube series dilution test, the reading being taken after 24 hours' incubation at 37°C.

The MIC is determined by the non-turbid test tube in the dilution series. A complete medium of the following composition was used as the growth medium:

Lab Lemco (Oxoid)	10 g
Peptone (Difco)	10 g
NaCl	3 g
D(+) Dextrose (Merck)	10 g
Buffer pH 7.4	1,000 ml

The penicillin unit (U) referred to in this Specification is the standard penicillin Unit; 1 mol of penicillin is equivalent to 5.9514×10^8U.

TABLE 1:
MIC in U/ml

Compound of Example No.	Bacterial strain												
	E. coli				*Proetus morg.*		*Psdm. aerug.*		*Klebsiella*		*Staph.*	*aureus*	Enterococcus ATCC 9790
	14	A 261	C 165	183/58	932	1017	F 41	Walter	K 10	63	1756	133	
Ampicillin	>1		8	200	256	256		>256		128	256	<1	4
1	4	>256	16	16	8	<32	32	16	64	64	64	<1	~8
2	4<16	>256	16<64	16<64	>256	64<256	16<64	>256	64<256	64<256	16<64	<1	4<16
3	4<16	>256	16<64	16<64	64<256	16<64	16<64	16<64	64<256	16<64	16<64	1<4	4<16
4	4<16	>256	16<64	16<64	>256	64<256	64<256	64<256	64<256	64<256	16<64	<1	4<16
5	8	>256	16	32	256	32	64	64	128	64	32	<1	16
6	4<16	>256	16<64	4<16	64<256	–	16<64	16<64	16<64	16<64	16<64	<1	16<64
7	<1	>256	8	8	256	32	32	32	32	32	64	<1	8
8	1<4	>256	8	16	128	64	64	64	64	32	8	<1	8

TABLE 1 (continued)
MIC in U/ml

Compound of Example No.	Bacterial strain												
	E. coli				*Proteus morg.*		*Psdm. aerug.*		*Klebsiella*		*Staph. aureus*		Enterococcus ATCC 9790
	14	A 261	C 165	183/58	932	1017	F 41	Walter	K 10	63	1756	133	
9	1<4	>256	16<64	4<16	64<256	–	16<64	16<64	16<64	16<64	64<256	<1	4<16
10	<1	>256	4<16	1<4	64<256	16<64	16<64	4<16	16<64	16<64	4<16	<1	~16
11	4	>256	8	8	128	64	32	32	64	32	128	<1	16
12	~4	>256	8	16	>256	16	32	32	32	32	16	<1	~8
13	<1	64<256	4<16	1<4	64<256	4<16	16<64	16<64	16<64	4<16	4<16	<1	4<16
14	<1	>256	~8	16	256	16	32	32	32	32	32	<1	8
15	1<4	>256	4<16	4<16	64<256	–	16<64	16<64	16<64	16<64	16<64	<1	4<16
16	~1	>256	8	8	256	64	16	16	32	16	64	<1	8

TABLE 1 (continued)
MIC in U/ml

Compound of Example No.	Bacterial strain											
	E. coli				*Prot. morg.*		*Psdm. aerug.*		*Klebsiella*		*Staph. aureus*		Entero–coccus ATCC
	14	A 261	C 165	183/58	932	1017	F 41	Walter	K 10	63	1756	133	9790
17	4	>256	~8	8	128	~32	32	32	64	32	32	<1	16
18	4	>256	8	8	128	64	16	16	64	64	16	<1	8
19	<1	>256	4<16	4<16	64<256	~16	16<64	4<16	16<64	16<64	1<4	<1	4<16
20	<1	~256	1<4	1<4	16<64	~4	4<16	~4	4<16	4<16	~4	<1	~4
21	<1	~256	4<16	~1	16<64	4<16	~16	4<16	16<64	16<64	4<16	<1	~4
22	1<4	>256	4<16	4<16	64<256	~16	16<64	4<16	16<64	16<64	4<16	<1	1<4
23	<1	64<256	1<4	<1	16<32	1<4	4<16	4<16	4<16	4<16	1<4	<1	4<16
24	1<4	>256	4<16	1<4	16<64	16<64	4<16	4<16	16<64	4<16	4<16	<1	1<4

TABLE 1 (continued)
MIC in U/ml

Compound of Example No.	Bacterial strain												
	E. coli				*Prot. morg.*		*Psdm. aerug.*		*Klebsiella*		*Staph. aureus*		Entero-coccus ATCC 9790
	14	A 261	C 165	183/58	932	1017	F 41	Walter	K 10	63	1756	133	
25	8	>256	16	8	16	128	16	32	64	32	64	<1	8
26	<1	256	4	<1	8	16	16	16	16	4	64	<1	16
27	1<4	>256	16<64	4<16	64<256	–	16<64	16<64	16<64	16<64	16<64	<1	4<16
28	<1	>256	4	4	128	16	16	16	16	16	~32	<1	4
29	<1	>256	4	16	>256	256	~32	32	128	64	32	<1	4
30	~32	>256	32	256	>256	>256	128	>256	>256	256	64	<1	8
Ampicillin	>1		8	200	256	256		>256		128	256	<1	4
31	4<16	>256	16<64	4<16	64<256	–	16<64	64<256	16<64	64<256	64<256	<1	4<16

TABLE 1 (continued)
MIC in U/ml

Compound of Example No.	Bacterial strain												
	E. coli				*Prot. morg.*		*Psdm. aerug.*		*Klebsiella*		*Staph. aureus*		Enterococcus ATCC
	14	A 261	C 165	183/58	932	1017	F 41	Walter	K 10	63	1756	133	9790
32	4<16	>256	16<64	16<64	64<256	–	16<64	64<256	64<256	16<64	16<64	<1	4<16
33	~8	>256	~32	32	256	64	64	128	128	128	32	<1	4
34	~16	>256	32	128	>256	128	64	256	256	128	32	<1	~4
35	<1	>256	4	<1	128	~1	4	4	16	8	8	<1	~4
36	8	>256	~16	32	128	128	32	~64	128	64	64	<1	8
37	4	>256	8	16	~128	128	~32	32	64	32	64	<1	16
38	4	>256	16	16	~256	32	32	32	128	64	32	<1	~16
39	4<16	>256	16<64	4<16	64<256	–	16<64	16<64	64<256	16<64	~64	<1	4<16

TABLE 1 (continued)
MIC in U/ml

Compound of Example No.	Bacterial strain												
	E. coli				*Prot. morg.*		*Psdm. aerug.*		*Klebsiella*		*Staph. aureus*		Enterococcus ATCC
	14	A 261	C 165	183/58	932	1017	F 41	Walter	K 10	63	1756	133	9790
40	1<4	>256	4<16	4<16	64<256	64<256	16<64	16<64	64<256	16<64	16<64	<1	4<16
41	8	>256	32	64	128	64	32	64	128	128	32	<1	8
42	4<16	>256	16<64	64<256	>256	>256	64<256	64<256	>256	64<256	4<16	<1	~4
43	~16	>256	16<64	64<256	>256	64<256	64<256	>256	64<256	64<256	64<256	<1	4<16
44	~8	256	16	128	>256	>256	~64	256	256	128	64	<1	4
45	<1	>256	8	4	128	16	8	16	32	16	16	<1	<1
Ampicillin	>1		8	200	256	256		>256		128	256	<1	4
46	<1	64<256	~4	1<4	64<256	16<64	4<16	4<16	16<64	16<64	1<4	<1	~4

TABLE 1 (continued)
MIC in U/ml

Compound of Example No.	Bacterial strain												
	E. coli				*Prot. mort*		*Psdm. aerug.*		*Klebsiella*		*Staph. aureus*		Enterococcus ATTC
	14	A 261	C 165	183/58	932	1017	F 41	Walter	K 10	63	1756	133	9790
47	16	>256	32	128	>256	32	64	>256	256	128	64	<1	4
48	1<4	64<256	4<16	4<16	64<256	64<256	16<64	16<64	16<64	16<64	4<16	<1	4<16
49	16<64	>256	64<256	64<256	>256	64<256	<256	>256	>256	>256	16<64	<1	4<16
50	16<64	>256	64<256	64<256	>256	–	>256	>256	>256	64<256	16<64	<1	16<64
51	~16	>256	16<64	16<64	>256	–	64<256	64<256	64<256	64<256	16<64	<1	4<16
52	32-64	>256	128-256	32-64	>256	>256	128-256	128-256	128-256	128-256	32-64	<1	32-64
53	32	>256	128-256	128-256	>256	>256	128-256	>256	>256	128-256	32-64	<1	2-4
54	4<16	>256	16<64	4<16	64<256	–	16<64	16<64	16<64	16<64	16<64	<1	16<64

TABLE 1 (continued)
MIC in U/ml

Compound of Example No.	Bacterial strain												
	E. coli				*Prot. morg.*		*Psdm. aerug.*		*Klebsiella*		*Staph. aureus*		Enterococcus ATCC
	14	A 261	C 165	183/58	932	1017	F 41	Walter	K 10	63	1756	133	9790
55	16>4	>256	64>16	64>16	>256	>256	64>16	256>64	256>64	256>64	64>16	<1	64>16
56	1<4	>256	4<16	4<16	64<256	16<64	4<16	4<16	16<64	16<64	4<16	<1	4<16
57	~1	>256	4<16	1<4	64<256	64<256	4<16	4<16	16<64	16<64	4<16	<1	4<16
58	~16	>256	64<256	16<64	>256	>256	64<256	64<256	64<256	64<256	4<16	<1	4<16
59	~4	>256	4<16	16<64	>256	4<16	>256	>256	64<256	16<64	4<16	<1	4<16
60	1<4	>256	4<16	16<64	64<256	~4	~256	64<256	16<64	16<64	1<4	1<4	4<16
Ampicillin	>1		8	200	256	256		>256		128	256	<1	4
61	1<4	>256	4<16	16<64	>256	64<256	64<256	>256	16<64	16<64	4<16	<1	~16

TABLE 1 (continued)
MIC in U/ml

Compound of Example No.	Bacterial strain												
	E. coli				*Proteus morg.*		*Psdm. aerug.*		*Klebsiella*		*Staph. aureus*		Entero-coccus ATCC
	14	A 261	C 165	183/58	932	1017	F 41	Walter	K 10	63	1756	133	9790
62	4<16	>256	16<64	16<64	64<256	4<16	64<256	16<64	16<64	16<64	16<64	1<4	4<16
63	~1	>256	16<64	64<256	>256	64<256	64<256	64<256	64<256	64<256	4<16	<1	~4
64	1<4	>256	32	64	>256	64	256	128	128	64	16	1<4	8
65	1<4	>256	16<64	16<64	>256	–	64<256	64<256	64<256	16<64	16<64	<1	4<16
66	8	>256	32	64	>256	32	64	128	64	32	32	<1	32
67	1<4	>256	16<64	4<16	>256	>256	64<256	64<256	16<64	16<64	16<64	<1	4<16
68	1<4	>256	16<64	4<16	64<256	–	64<256	64<256	16<64	16<64	16<64	<1	16<64
69	1<4	>256	16<64	16<64	64<256	–	64<256	64<256	16<64	16<64	16<64	<1	4<16

TABLE 1 (continued)
MIC in U/ml

Compound of Example No.	Bacterial strain												
	E. coli				*Proteus morg.*		*Psdm. aerug.*		*Klebsiella*		*Staph. aureus*		Enterococcus ATCC
	14	A 261	C 165	183/58	932	1017	F 41	Walter	K 10	63	1756	133	9790
70	4<16	>256	16<64	64<256	>256	–	64<256	>256	64<256	64<256	16<64	<1	16<64
71	<4	>256	4<16	64<256	>256	64<256	16<64	64<256	64<256	64<256	16<64	<1	4<16
72	1<4	>256	4<16	4<16	>256	64<256	64<256	64<256	16<64	16<64	16<64	<1	<16
73	4<16	>256	16<64	4<16	64<256	–	64<256	64<256	64<256	16<64	64<256	<1	16<64
74	4<16	>256	16<64	64<256	>256	–	64<256	>256	>256	64<256	16<64	<1	4<16
75	4<16	>256	16<64	16<64	>256	–	16<64	64<256	64<256	64<256	16<64	<1	<16
76	<4	>256	16<64	16<64	>256	64<256	>256	>256	16<64	16<64	4<16	<1	<16
Ampicillin	>1		8	200	256	256		>256		128	256	<1	4

This table shows that the new compounds display strong anti-bacterial effects. Their activity extends to both Gram-positive and Gram-negative bacteria, of which the following families of bacteria, genera of bacteria and varieties of bacteria may be mentioned as examples: from the family of the *Enterobacteriaceae*, for example *Escherichia* (especially *Escherichia coli*), *Klebsiella* (especially *Klebsiella pneumoniae*) and *Enterobacter aerogenes*, *Serratia Proteus* (especially *Proteus vulgaris*, *Proteus mirabilis*, *Proteus morganii* and *Proteus rettgeri*) and *Salmonella* (especially *Salmonella enteritidis*;

From the family of the *Micrococcaceae*, for example *Staphylococcus aureus* and *Staphylococcus epidermidis*;

from the family of the *Lactobacteriaceae*, for example *Streptococcus pyogenes* and *Streptococcus faecalis* (Enterococcus).

The new penicillins have proved especially effective in the therapy of infections caused by *Klebsiella*, *Proteus* and *Pseudomonas* bacteria (see Table 2).

The following experiment was carried out with the penicillin from Example 1A:

The penicillin of Example 1A was diluted with Müller-Hinton nutrient broth, with addition of 0.1% of glucose, per content of 100 μg/ml. The nutrient solution contained 1×10^5 to 2×10^5 bacteria per millilitre in each case. The test tubes containing this mixture were each incubated for 24 hours and thereafter the degree of turbidity was determined. The absence of turbidity showed an effect. At a dosage of 100 μg/ml, the following bacterial cultures were non-turbid:

E. coli 14; *E. coli* c165; *Proteus vulgaris* 1017; *Klebsiella* K 10; *Klebsiella* 63; *Salmonella* sp.; *Shigella* sp.; *Enterobacter* sp.; *Serratia* sp.; *Proteus*, indole-negative, sp.; *Proteus*, indole-positive, sp.; *Pasteurella pseudo-tuberculosis*; *Brucella* sp.; *Haemophilus influenzae*; *Bordetella bronchiseptica*; *Bacteroides* sp.; *Staphylococcus aureus* 133; *Neisseria cartarrhalis* sp.; *Diplococcus pneumoniae* sp.; *Streptococcus pyogenes* W; *Enterococcus* sp.; *Lactobacillus* sp.; *Corynebacterium diphteriae gravis*; *Corynebacterium pyogenes* M; *Clostridium botulinium*; *Clostridium tetani*; *Borrelia* sp.; *Pseudomonas aeruginosa* sp.; *Aeromonas hydrophila* sp.

TABLE 2:
Data from animal experiment

	Surviving animals (%) on:	
Bacterium and subcutaneous dose in Units per experiment animal	1st 2nd 3rd 5th day after infection Carbenicillin	1st 2nd 3rd 5th day after infection Compound of invention:
Klebsiella 62 2×3000	0	Compound of Ex. 1: 100 100 50 50
Klebsiella 63 2 × 3000	0	Compound of Ex. 7: 100 100 20 —
Psdm. aerug. F 41 4 × 3000	50 0	Compound of Ex.22: 80 80 80 —
Psdm. aerug. F 41 4 × 3000	80 30 30 20	Compound of Ex.29: 100 80 70 70
Klebsiella 63 2 × 3000	0	Compound of Ex.41: 80 50 50 50

Test animal: white mouse (Winkelmann)
Infection: intraperitoneal

The excellent and broad anti-bacterial activity of the new penicillins permits their use both in human medicine and in veterinary medicine, and they can be used both for preventing systemic or local bacterial infections and for treating such infections which have already occurred.

As stated above, the invention therefore also relates to the use in human and veterinary medicine of the compounds of the invention.

The present invention provides a pharmaceutical composition containing as active ingredient a compound of the invention in admixture with a solid or liquefied gaseous diluent, or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 (preferably less than 350) except in the presence of a surface active agent.

The invention further provides a pharmaceutical composition containing as active ingredient a compound of the invention in the form of a sterile or isotonic aqueous solution.

The invention also provides a medicament in dosage unit form comprising a compound of the invention either alone or in admixture with a diluent.

The invention also provides a medicament in the form of tablets (including lozenges and granules), dragees, capsules, pills, ampoules or suppositories comprising a compound of the invention either alone or in admixture with the diluent.

"Medicament" as used in this Specification means physically discrete coherent portions suitable for medical administration. "Medicament in dosage unit form" as

used in this Specification means physically discrete coherent portions suitable for medical administration each containing a daily dose or a multiple (up to four times) or sub-multiple (down to a fortieth) of a daily dose of the compound of the invention. Whether the medicament contains a daily dose or, for example, a half, a third, or a quarter of a daily dose will depend on whether the medicament is to be administered once or, for example, twice, three times or four times a day respectively.

The pharmaceutical compositions according to the invention may, for example, take the form of ointments, gels, pastes, creams, sprays (including aerosols), lotions, suspensions, solutions and emulsions of the active ingredient in aqueous or non-aqueous diluents, syrups, granules or powders.

The diluents to be used in pharmaceutical compositions (e.g. granulates) adapted to be formed into tablets, dragees, capsules and pills include the following:—

(a) fillers and extenders, e.g. starch, sugars, mannitol, and silicic acid; (b) binding agents, e.g. carboxymethyl cellulose and other cellulose derivatives, alginates, gelatine and polyvinyl pyrrolidone; (c) moisturizing agents, e.g. glycerol; (d) disintegrating agents, e.g. agar-agar, calcium carbonate and sodium bicarbonate; (e) agents for retarding dissolution e.g. paraffin; (f) resorption accelerators, e.g. quaternary ammonium compounds; (g) surface active agents, e.g. cetyl alcohol, glycerol monostearate; (h) adsorptive carriers, e.g. kaolin and bentonite; (i) lubricants, e.g. talc, calcium and magnesium stearate and solid polyethylene glycols.

The tablets, dragees, capsules and pills formed from the pharmaceutical compositions of the invention can have the customary coatings, envelopes and protective matrices, which may contain opacifiers. They can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes and protective matrices may be made, for example, of polymeric substances or waxes.

The ingredient can also be made up in microencapsulated form together with one or several of the above-mentioned diluents.

The diluents to be used in pharmaceutical compositions adapted to be formed into suppositories can, for example, be the usual water-soluble or water-insoluble diluents, such as polyethylene glycols and fats (e.g. cocoa oil and high esters [e.g. C_{14}-alcohol with C_{16}-fatty acid]) or mixtures of these diluents.

The pharmaceutical compositions which are ointments, pastes, creams and gels can, for example, contain the usual diluents, e.g. animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide or mixtures of these substances.

The pharmaceutical compositions which are powders and sprays can, for example, contain the usual diluents, e.g. lactose, talc, silicic acid, aluminium hydroxide, calcium silicate, and polyamide powder or mixtures of these substances. Aerosol sprays can, for example, contain the usual propellants, e.g. chlorofluorohydrocarbons.

The pharmaceutical compositions which are solutions and emulsions can, for example, contain the customary diluents (with, of course, the above-mentioned exclusion of solvents having a molecular weight below 200 except in the presence of a surface-active agent), such as solvents, dissolving agents and emulsifiers; specific examples of such diluents are water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils [for example ground but oil], glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitol or mixtures thereof.

For parenteral administration, the solutions and emulsions should be sterile, and, if appropriate, blood-isotonic.

The pharmaceutical compositions which are suspensions can contain the usual diluents, such as liquid diluents, e.g. water, ethyl alcohol, propylene glycol, surface-active agents (e.g. ethoxylated isostearyl alcohols, polyoxyethylene sorbite and sorbitane esters), microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth or mixture thereof.

All the pharmaceutical compositions according to the invention can also contain colouring agents and preservatives as well as perfumes and flavouring additions (e.g. peppermint oil and eucalyptus oil) and sweetening agents (e.g. saccharin).

The pharmaceutical compositions according to the invention preferably contain about 0.1 to 99.5, more preferably from about 0.5 to 95% of the active ingredient by weight of the total composition.

In addition to a compound of the invention, the pharmaceutical compositions and medicaments according to the invention can also contain other pharmaceutically active compounds. They may also contain a plurality of compounds of the invention.

Any diluent in the medicaments of the present invention may be any of those mentioned above in relation to the pharmaceutical compositions of the present invention. Such medicaments may include solvents of molecular weight less than 200 as sole diluent.

The discrete coherent portions constituting the medicament according to the invention (whether in dosage unit form or not) may be, for example, any of the following: tablets, (including lozenges and granules), pills, dragees, capsules, suppositories and ampoules. Some of these forms may be made up for delayed release of the active ingredient. Some, such as capsules, include a protective envelope which renders the portions of the medicament physically discrete and coherent.

The preferred daily dose for oral and parenteral administration of the medicaments of the invention is 1.25×10^6 to 90×10^6U of active ingredient.

The production of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredient(s) with the diluent(s) to form a pharmaceutical composition (e.g. a granulate) and then forming the composition into the medicament (e.g. tablets).

This invention further provides a method of combating (including prevention, relief and cure of) the above-mentioned diseases in human and non-human animals, which comprises administering to the animals a compound of the invention alone or in admixture with a diluent or in the form of a medicament according to the invention.

It is envisaged that these active compounds will be administered in the customary way for antibiotics, generally perorally, parenterally (for example intramuscularly, intraperitoneally or intravenously) or locally. Preferred pharmaceutical compositions and medicaments are therefore those adapted for peroral, parenteral and local administration, such as tablets, capsules, injectable solutions, ampoules of injectable solutions, ointments and impregnated gauzes. Administration in the method of the invention is preferably peroral or parenteral.

In general it has proved advantageous to administer amounts of from 25,000—1,000,000 U/kg of body weight per day to achieve effective results. Nevertheless, it can at times be necessary to deviate from those dosage rates, and in particular to do so as a function of the nature and body weight of the human or animal subject to be treated, the individual reaction of this subject to the treatment, the type of formulation in which the active ingredient is administered and the mode in which the administration is carried out, and the point in the progress of the disease or interval at which it is to be administered. Thus it may in some case suffice to use less than the above-mentioned minimum dosage rate, whilst other cases the upper limit mentioned must be exceeded to achieve the desired results. Where larger amounts are administered it can be advisable to divide these into several individual administrations over the course of the day.

When used as feedstuff additives, the new compounds can be given in the form of medicated fodder comprising an animal feedstuff and a compound according to the invention, or with the drinking water. This makes it possible to prevent an infection by Gram-negative or Gram-positive bacteria and equally to achieve better utilisation of the feedstuff. The new penicillins can be combined with other substances, so as to raise the antibacterial effect. A raising of the effect can for example be brought about by inhibiting the decomposition of the compounds according to the invention, e.g. by the addition of isoxazolyl-penicillins.

Preparative Examples.

The following Examples illustrate the production of compounds according to the invention by the process according to the invention.

The β-lactam content of the penicillins was determined iodometrically and in some cases by means of IR spectroscopy.

All N-acylated aromatic amino acids of the general structural formulae VII to XIV were examined by thin layer chromatography on DC plates with silica gel F—254 (Messrs. Merck, Darmstadt).

The following served as migrating agents:

SBA:	75	% by volume of	sec.-butanol
	13.5	" " " "	90 per cent strength formic acid
	11.5	" " " "	water
SBN:	85	% by volume of	sec.-butanol
	15	" " " "	10 per cent strength ammonia

PEW: n-propanol/ethyl acetate water (4:3:3)

CMA: 95 % by volume of chloroform
5 " " " " methanol
3 " " " " glacial acetic acid.

Compounds with a free amino group were rendered visible by spraying with a 5 per cent strength solution of ninhydrin in a mixture of n-butanol and 2 N acetic acid (95:5, V/V) and brief heating in a drying cabinet (80—100°C). More frequently, however, the chlorine/tolidine reaction — spraying with tert.-butyl hypochlorite and subsequently (after brief heating) with a solution of o-tolidine and potassium chloride containing acetic acid — was used. [Literature: R. H. Mazur, B. W. Ellis and P. S. Cannaratu, J. biol. Chemistry *237*, 1619 (1962) and E. von Arx and R. Neher, J. Chromatogr. (Amsterdam) *12*, 329 (1963)].

All intermediate compounds and penicillin derivatives described here show an IR spectrum corresponding to their structure.

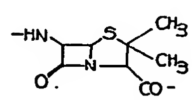
All the compounds were subjected to an analytical counter-current distribution over the course of 29 hours, using petroleum ether/ethyl acetate/dimethylformamide/water (3:7:5:5) as the distribution system.

The NMR spectra of penicillins were recorded in CD_3OD solution.

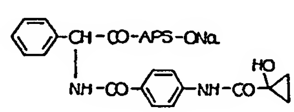
In calculating the elementary analyses, the water content of the penicillins has been taken into account.

The figures (U/ml) quoted for the reactivities against bacterial strains are minimum inhibitory concentrations in the test tube series dilution test after 24 hours' incubation.

Throughout the Examples, "APS" denotes the aminopenicillamic acid residue:



Example 1.



A) 10 g (0.027 mol) of sodium D-α-aminobenzylpenicillin [= sodium ampicillin or sodium 6-(α-aminophenylacetylamino)-penicillanate] were dissolved in 100 ml of THF with addition of 20 ml of water. After cooling the reaction mixture to between 0° and 5°C, 7.5 g (0.0336 mol) of 4-cyclopropanecarbonylamino-benzoyl chloride dissolved in 40 ml of THF were added dropwise over the course of 30 minutes whilst cooling with ice/water and keeping the pH value at between 7.5 and 7.8 by simultaneous addition of 2 N sodium hydroxide solution. The mixture was stirred for 30 minutes at 0° to 5° and subsequently for 2.5 hours at room temperature, during which time the pH value was kept constant at 7.5 by adding a little 2 N sodium hydroxide solution. After distilling off the THF, a viscous mass remained, which was dissolved in 300 ml of water and extracted once with ethyl acetate.

The aqueous phase was separated off, cooled to 0°, covered with 250 ml of ethyl acetate and acidified with 2 N HCl to a pH value of 2.0. The organic phase was separated off and the aqueous phase was extracted twice more with 80 ml of ethyl acetate. The combined ethyl acetate extracts were washed with water until neutral and dried over Na_2SO_4 in a refrigerator. After evaporating off the solvent, a light resinous product remained, which was taken up in 80 ml of absolute methanol and treated with an equivalent proportion of a 1-molar solution of sodium 2-ethyl-hexanoate in ether containing methanol. The solution was gently concentrated to dryness *in vacuo* and the residue was recrystallised from 90 ml of absolute methanol and 600 ml of absolute ether.

Yield relative to sodium ampicillin: 9.4 g (62.5%) of sodium D-α-(4-cyclopropanecarbonylamino-benzoylamino)-benzylpenicillin:

β-Lactam content: 91.7%

$C_{27}H_{27}N_4O_6SNa \cdot 1H_2O$ (576.6)

Calculated.	C 56.24	H 4.89	N 9.72	S 5.58
Found.	C 55.2	H 5.4	N 9.2	S 6.0

B) 4-Cyclopropanecarbonylamino-benzoic acid.

20 g (0.146 mol) of p-aminobenzoic acid (PAB) were dissolved in 80 ml of THF and 20.4 ml (0.146 mol) of triethylamine were next added to the solution. Thereafter, 22.5 g (0.216 mol) of cyclopropanecarboxylic acid chloride in 40 ml of THF were rapidly added dropwise whilst cooling with ice. At the end of the dropwise addition, a further 9.4 ml of triethylamine were introduced all at once into the suspension (pH= 7 to 8). The reaction solution was boiled for 5 hours under reflux and then cooled to room temperature, and thereafter the solvent was distilled off *in vacuo*. The residue which remained was dissolved in water and the resulting solution was rendered acid with 2 N HCl (pH 2.0). The residue was filtered off, thoroughly washed with water on the filter and finally dried in air. It was recrystallised from THF/petroleum ether.

Yield: 28.0 g (93.6%)

$C_{11}H_{11}NO_3$ (205.2)

Calculated.	C 64.39	H 5.40	N 6.82
Found.	C 64.9	H 5.6	N 6.0

C) 4-Cyclopropanecarbonylamino-benzoyl chloride.

12 g (0.0585 mol) of 4-cyclopropanecarbonylamino-benzoic acid were suspended in 35 g of analytical grade benzene. The mixture was treated for several hours with 17 g of thionyl chloride and 0.2 ml of DMF at 60°C, until the evolution of gas had ceased. The solution was concentrated to dryness *in vacuo*, the residue was dissolved in THF and the solvent was distilled off completely.

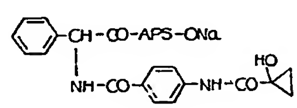
Yield: 9.5 g (73%)

$C_{11}H_{10}ClNO_2$ (223.7)

Calculated.	C 59.06	H 4.51	N 6.26	Cl 15.85
Found.	C 58.01	H 4.8	N 5.5	Cl 15.5

NMR signals at δ: 1.0—1.3 ppm (5H) 7.6—8.2 ppm (4H)

Example 2.



A) Condensation:

The cold solution of the unsymmetrical anhydride, prepared according to B, was treated at −15°C with the solution of the amine component, prepared according to C, which was also cooled. The mixture was stirred overnight with the temperature gradually rising from −15° to +15°. On the following day the solvent was stripped off *in vacuo* (bath temperature 20°), the residue was stirred with 300 ml of water and the solution thereby produced was extracted once with ethyl acetate. The aqueous phase was cooled to 0°, covered with 200 ml of ethyl acetate and acidified with 2 N HCl. The aqueous solution was extracted twice more with 100 ml of ethyl acetate at a time. The combined organic solvent extracts were thoroughly washed with water and thereafter dried over Na_2SO_4 in a refrigerator. After filtration, the solution was concentrated *in vacuo*, reacted with an equivalent amount of a 1-molar solution of sodium 2-ethylhexanoate in ether containing methanol, and the mixture was left to stand for 10 minutes at 0°C. Thereafter the solvent was distilled off and the resulting semi-solid mass was reprecipitated from 90 ml of analytical grade methanol and 600 ml of analytical grade ether, filtered off and dried for 5 hours in a desiccator over P_2O_5 by means of a high vacuum.

Yield relative to the carboxyl component B: 8.4 g (70.5%) of sodium D-α-(4-cyclopropanol-1-carbonyl-amino-benzoylamino)-benzylpenicillin:

$C_{27}H_{27}N_4O_7SNa \cdot 2H_2O$ (610.6):

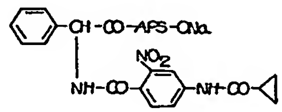
Calculated:	C 53.11	H 5.11	N 9.17	S 5.26
Found:	C 52.5	H 5.9	N 8.3	S 5.5

β-Lactam content: 93.8%
NMR signals at δ: 1.1—1.4 (4H); 1.5 (6H); 4.1 (1H); 4.2 (1H); 5.5 (2H); 5.9 (1H); 7.3—7.4 ppm (9H).

B) Activation of the carboxyl component:
4.6 g (0.0208 mol) of 4-(1-hydroxycyclopropanecarbonylamino)-benzoic acid were dissolved in 20 ml of absolute DMF and 40 ml of absolute THF, 2.35 ml (0.021 mol) of N-methylmorpholine were added followed, after cooling to −15°C, by 2.1 ml (0.0218 mol) of chloroformic acid ethyl ester, and the mixture was stirred for 15 minutes at −15° to −10°C.

C) Preparation of the amine component:
8.7 g (0.025 mol) of D-α-aminobenzylpenicillin (= ampicillin) were suspended in 70 ml of CH_2Cl_2 and 5.6 ml (0.04 mol) of triethylamine in the presence of anhydrous Na_2SO_4 at −10° and the mixture was then stirred for 1.5 hours at room temperature. Thereafter the solution was freed of the Na_2SO_4 by filtration and was stored at −10°C for the next reaction step.

Example 3.



A) This penicillin was synthesised as described in Example 2 by the mixed anhydride method from 29 g (0.0116 mol) of 4-cyclopropanecarbonylamino-2-nitro-benzoic acid, 1.4 ml (0.0125 mol) of N-methylmorpholine and 1.2 ml (0.0125 mol) of chloroformic acid ethyl ester.

4.89 g (0.014 mol) of ampicillin and 3.14 ml (0.0224 mol) of triethylamine were used as the amine component.

Yield: 5.1 g (74%) of sodium D-α-(4-cyclopropanecarbonylamino-2-nitrobenzoylamino)-benzylpenicillin:

$C_{27}H_{26}N_5O_8SNa \cdot 2H_2O$ (639.6)

Calculated:	C 50.70	H 4.72	N 10.95	S 5.02
Found:	C 51.0	H 6.1	N 10.0	S 5.7

β-Lactam content: 93.2%

B) 4-Cyclopropanecarbonylamino-2-nitrobenzoic acid
6 g (0.033 mol) of 4-amino-2-nitrobenzoic acid were dissolved in a mixture (100 ml) of THF and water (1:1). The solution was adjusted to pH 8.5 with 2 N NaOH and reacted at room temperature with 3.78 g (0.0363 mol) of cyclopropane-carboxylic acid chloride in 25 ml of THF. The pH value of the reaction solution was kept at 8.0—8.5 to the end by further addition of 2 N sodium hydroxide solution. After a reaction time of 3.5 hours, the solvent was next distilled off. The residue was diluted with water and the aqueous solution was extracted by shaking once with ethyl acetate and was finally acidified with 2 N HCl to pH 2.0. The oil which precipitated was isolated by extraction with ethyl acetate. After washing and drying the ethyl acetate phase, the solution was concentrated to dryness. The product was crystallised from ethyl acetate/petroleum ether.

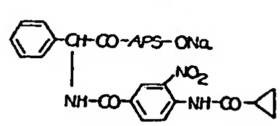
Thin layer chromatography: a single product in PEW, SBA and CMA.

Yield: 3.0 g (36.4%)

$C_{11}H_{10}N_2O_5$ (250.2)

Calculated.	C 52.81	H 4.03	N 11.20
Found.	C 51.9	H 4.2	N 11.4

Example 4.



A) This penicillin was prepared as described in Example 2 from 6.32 g (0.0252 mol) of 4-cyclopropanecarbonylamino-3-nitro-benzoic acid, 2.94 ml (0.0262 mol) of N-methyl-morpholine, 2.52 ml (0.0262 mol) of chloroformic acid ethyl ester and 10.6 g (0.0302 mol) of ampicillin and 6.85 ml (0.049 mol) of TEA.

Yield: 10.2 g (67%) of sodium D-α-(4-cyclopropanecarbonylamino-3-nitro-benzoylamino)-benzylpenicillin:

$C_{27}H_{26}N_5O_8SNa \cdot 2H_2O$ (639.6)

Calculated.	C 50.7	H 4.72	N 10.95	S 5.02
Found.	C 47.8	H 5.0	N 10.1	S 5.3

β-Lactam content: 84.9%.

B) 4-Cyclopropanecarbonylamino-3-nitro-benzoic acid

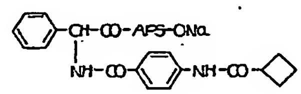
The acylation of 7.0 g (0.0384 mol) of 3-nitro-4-amino-benzoic acid with 4.42 g (0.0423 mol) of cyclopropanecarboxylic acid chloride was carried out as described in Example 3.

Yield: 6.4 g (66.6%)

$C_{11}H_{10}N_2O_5$ (250.2)

Calculated.	C 52.81	H 4.01	N 11.20
Found.	C 50.4	H 4.0	N 11.7

Example 5.



A) The penicillin was produced as described in Example 2 from:

1) 5.29 g (0.0239 mol) of 4-cyclobutanecarbonylamino-benzoic acid, 2.78 ml (0.0248 mol) of N-methylmorpholine and 2.38 ml (0.0248 mol) of chloroformic acid ethyl ester.
2) 10.0 g (0.0286 mol) of ampicillin and 6.47 ml (0.0462 mol) of triethylamine.

Yield: 11.6 g (84.7%) of sodium D-α-(4-cyclobutanecarbonylaminobenzoyl-amino)-benzylpenicillin:

$C_{28}H_{29}N_4O_6SNa \cdot 2H_2O$ (608.648)

Calculated.	C 55.26	H 5.46	N 9.20	S 5.28
Found.	C 54.5	H 6.4	N 8.8	S 5.8

β-Lactam content: 97.7%.

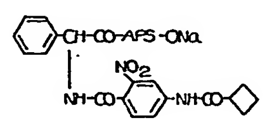
B) 4-Cyclobutanecarbonylamino-benzoic acid was prepared as described in Example 3 from 7.05 g (0.0514 mol) of *p*-aminobenzoic acid (PAB) and 6.4 g (0.054 mol) of cyclobutanecarboxylic acid chloride.

Yield: 6.7 g (59.4%)

$C_{12}H_{13}NO_3$ (219.243)

Calculated.	C 65.75	H 5.98	N 6.39
Found.	C 64.2	H 6.0	N 6.1

Example 6.



A) The penicillin was prepared as described in Example 2 from:

1) 5.5 g (0.0208 mol) of 4-cyclobutanecarbonylamino-2-nitrobenzoic acid, 2.46 ml (0.022 mol) of N-methylmorpholine and 2.11 ml (0.022 mol) of chloroformic acid ethyl ester.
2) 8.72 g (0.025 mol) of ampicillin and 5.6 ml (0.04 mol) of triethylamine.

Yield: 8.8 g (68.8%) of sodium D-α-(4-cyclobutanecarbonylamino-2-nitro-benzoylamino)-benzylpenicillin:

$C_{25}H_{25}N_5O_8SNa \cdot 2H_2O$ (653.646)

Calculated.	C 51.45	H 4.93	N 10.71	S 4.91
Found.	C 52.4	H 5.8	N 10.1	S 5.3

β-Lactam content: 91.0%.

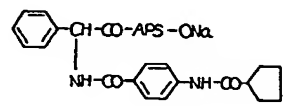
B) 4-Cyclobutanecarbonylamino-2-nitro-benzoic acid was prepared as described in Example 3 from 10.9 g (0.06 mol) of 4-amino-2-nitro-benzoic acid and 7.83 g (0.066 mol) of cyclobutanecarboxylic acid chloride.

Yield: 6.3 g (the product was recrystallised from ethyl acetate/petroleum ether).

$C_{12}H_{12}N_2O_5$ (264.240)

Calculated.	C 54.56	H 4.58	N 10.60
Found.	C 54.2	H 4.9	N 10.60

Example 7.



A) 8.1 g (0.0323 mol) of 4-cyclopentanecarbonylamino-benzoyl chloride were reacted with 10.0 g (0.0269 mol) of sodium D-α-aminobenzylpenicillin (sodium ampicillin) as described in Example 1.

Yield: 14 g (88.5%) of sodium D-α-(4-cyclopentanecarbonylamino-benzoyl-amino)-benzylpenicillin.

B) 4-Cyclopentanecarbonylamino-benzoic acid was prepared as described in Example 1B from 31.5 g (0.23 mol) of p-aminobenzoic acid and 17.3 g (0.23 mol) of cyclopropanecarboxylic acid chloride in the presence of triethylamine.

Yield: 31.8 g (59.5%); product reprecipitated from THF/petroleum ether.

$C_{13}H_{15}NO_3$ (233.270)

Calculated.	C 66.93	H 6.48	N 6.00
Found.	C 66.4	H 6.6	N 5.8

C) 4-Cyclopentanecarbonylamino-benzoyl chloride:

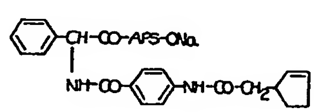
25.9 g (0.111 mol) of 4-cyclopentane-carbonylamino-benzoic acid were converted into the acid chloride by means of 12.1 ml (0.166 mol) of thionyl chloride in the presence of CH_2Cl_2, whilst boiling under reflux.

Yield: 26 g (94%)

$C_{13}H_{14}NO_2Cl$ (251.713)

Calculated.	C 62.03	H 5.61	N 5.57	Cl 14.08
Found.	C 60.4	H 5.6	N 5.6	Cl 13.3

Example 8.



A) The penicillin was prepared as described in Example 2 from:

1) 5.85 g (0.0239 mol) of 4-(2-cyclopentene-1-acetamido)-benzoic acid, 2.78 ml (0.0248 mol) of N-methylmorpholine and 2.38 ml (0.0248 mol) of chloroformic acid ethyl ester.

2) 10.0 g (0.0286 mol) of ampicillin and 6.47 ml (0.0462 mol) of triethylamine.

Yield: 10.0 g (70%) of sodium D-α-(4-[2-cyclopentene-1-acetamido-benzoyl-amino])-benzylpenicillin

$C_{30}H_{31}N_4O_8SMg \cdot 2H_2O$ (634.7)

Calculated.	C 56.78	H 5.56	N 8.83	S 5.06
Found.	C 56.7	H 5.7	N 8.1	S 4.5

β-Lactam content: 98.2%

B) 4-(2-Cyclopentene-1-acetamido)-benzoic acid was prepared as described in Example 3 from 8.25 g (0.06 mol) of p-aminobenzoic acid and 9.5 g (0.067 mol) of 2-cyclopentene-1-acetyl chloride.

Yield: 13.3 g (90.5%)

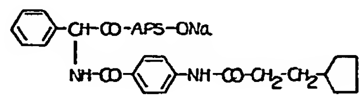
Thin layer chromatogram: a single substance in PEW, SBA and MCA (ninhydrin negative)

$C_{14}H_{15}NO_3$ (245.3)

Calculated.	C 68.56	H 6.16	N 5.71
Found.	C 63.0	H 5.7	N 5.3

NMR signals at δ = 7.7—8.1 (4H), 5.8 (2H), 2.5 (2H), 2.0—2.4 ppm (5H)

Example 9.



A) The penicillin was prepared as described in Example 2 from:

1) 6.64 g (0.0239 mol) of 4-(3-cyclopentylpropionylamino)-benzoic acid, 2.78 ml (0.0248 mol) of N-methylmorpholine and 2.38 ml (0.0248 mol) of chloroformic acid ethyl ester.
2) 10.0 g (0.0286 mol) of ampicillin and 6.47 ml (0.0462 mol) of triethylamine.

Yield: 10.8 g (73.5%) of sodium D-α-[4-(3-cyclopentylpropionylaminobenzoylamino)]-benzylpenicillin:

$C_{31}H_{35}N_4O_6SNa \cdot 3H_2O$ (668.7)

Calculated.	C 55.68	H 6.18	N 8.38	S 4.81
Found.	C 54.6	H 6.1	N 7.8	S 5.4

β-Lactam content: 89.3%

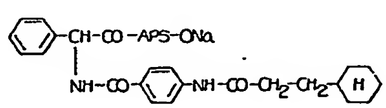
B) 4-(3-Cyclopentylpropionylamino)-benzoic acid was prepared as described in Example 3 from 9.63 g (0.07 mol) of p-aminobenzoic acid and 12.4 g (0.077 mol) of 3-cyclopentylpropionyl chloride.

Yield: 12.0 g (65.6%)

$C_{15}H_{19}NO_3$ (261.3)

Calculated.	C 68.95	H 7.33	N 5.36
Found.	C 68.8	H 7.5	N 5.4

Example 10.



A) The penicillin was prepared as described in Example 2 from:

1) 6.6 g (0.024 mol) of 4-(3-cyclohexanepropionylamino)-benzoic acid, 2.78 ml (0.0248 mol) of N-methylmorpholine and 2.38 ml (0.0248 mol) of chloroformic acid, ethyl ester.
2) 10.0 g (0.0286 mol) of ampicillin and 6.47 ml (0.0462 mol) of triethylamine.

Yield: 10.8 g (66.5%) of sodium D-α-[4-(3-cyclohexanepropionylamino-benzoylamino)]-benzylpenicillin:

$C_{32}H_{37}N_4O_6SNa \cdot 2H_2O$ (664.8)

Calculated.	C 57.82	H 6.21	N 8.43	S 4.83
Found.	C 56.8	H 6.9	N 8.0	S 5.4

β-Lactam content: 88.6%

B) 4-(3-Cyclohexanepropionylamino)-benzoic acid was prepared as described in

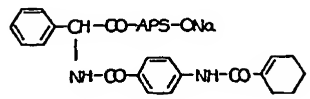
Example 3 from 10.0 g (0.073 mol) of *p*-aminobenzoic acid and 14.0 g (0.08 mol) of 3-cyclohexanepropionyl chloride.

Yield: 15.8 g (79%)

$C_{16}H_{21}NO_3$ (275.4)

Calculated. C 69.78 H 7.69 N 5.08
Found. C 68.9 H 7.0 N 4.2

Example 11.



A) The penicillin was prepared as described in Example 2 from:

1) 7 g (0.0286 mol) of 4-(1-cyclohexene-1-carbonylamino)-benzoic acid, 3.2 ml (0.0286 mol) of N-methylmorpholine and 2.74 ml (0.0286 mol) of chloroformic acid ethyl ester.
2) 12 g (0.0343 mol) of ampicillin and 7.67 ml (0.0549 mol) of triethylamine.

Yield: 14.0 g (82%) of sodium D-α-[4-(1-cyclohexene-1-carbonylamino-benzoylamino)]-benzylpenicillin:

$C_{30}H_{31}N_4O_6SNa$. $2H_2O$ (634.7)

Calculated. C 56.78 H 5.56 N 8.83 S 5.06
Found. C 56.0 H 5.6 N 7.9 S 5.3

β-Lactam content: 88.0%

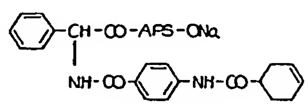
B) 4-(1-Cyclohexene-1-carbonylamino)-benzoic acid was prepared as described in Example 1 from 16.6 g (0.121 mol) of p-aminobenzoic acid with 22.0 g (0.152 mol) of 1-cyclohexene-1-carboxylic acid chloride and 21.3 mi (0.152 mol) of triethylamine. Recrystallisation from THF/n-pentane.

Yield: 15.0 g (50.5%)

$C_{14}H_{15}NO_3$ (245.3)

Calculated. C 68.56 H 6.16 N 5.71
Found. C 68.5 H 6.2 N 5.9

Example 12.



A) The penicillin was prepared as described in Example 2 from:

1) 5.85 g (0.0239 mol) of 4-(3-cyclohexene-1-carbonylamino)-benzoic acid, 2.69 mol (0.024 mol) of N-methylmorpholine and 2.3 ml (0.024 mol) of chloroformic acid ethyl ester.
2) 10 g (0.0286 mol) of ampicillin and 6.45 ml (0.046 mol) of triethylamine.

Yield: 8.8 g (60.7%) of sodium D-α-[4-(3-cyclohexene-1-carbonylamino-benzoylamino)]-benzylpenicillin:

$C_{30}H_{31}N_4O_6SNa$. $2H_2O$ (634.7)

Calculated. C 56.78 H 5.56 N 8.83 S 5.06
Found. C 56.5 H 5.5 N 7.7 S 4.4

β-Lactam content: 72.8%

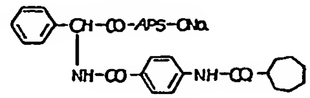
B) 4-(3-Cyclohexene-1-carbonylamino)-benzoic acid was prepared as described in Example 3 from 12 g (0.0875 mol) of p-aminobenzoic acid and 13.9 g (0.0963 mol) of 3-cyclohexene-1-carboxylic acid chloride.

Yield: 17.2 g (80.5%)

$C_{14}H_{15}NO_3$ (245.3)

Calculated. C 68.56 H 6.16 N 5.71
Found. C 67.2 H 5.9 N 5.2

Example 13.



A) The penicillin was prepared as described in Example 2 from:

1) 7.0 g (0.0268 mol) of 4-cycloheptanecarbonylamino-benzoic acid, 3.0 ml (0.0268 mol) of N-methylmorpholine and 2.58 ml (0.0268 mol) of chloroformic acid ethyl ester.

2) 11.2 g (0.0322 mol) of ampicillin and 7.2 ml (0.0515 mol) of triethylamine.

Yield: 12.0 g (73.0%) of sodium D-α-(4-cycloheptanecarbonylamino-benzoylamino)-benzylpenicillin

$C_{31}H_{35}N_4O_6SNa \cdot 3H_2O$ (668.7)

Calculated.	C 55.68	H 6.18	N 8.38	S 4.80
Found.	C 54.8	H 6.2	N 8.0	S 5.4

β-Lactam content: 92.3%

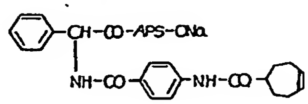
B) 4-Cycloheptanecarbonylamino-benzoic acid was prepared as described in Example 3 from 5.55 g (0.0405 mol) of *p*-aminobenzoic acid and 8.7 g (0.0425 mol) of cycloheptanecarboxylic acid chloride.

Yield: 9.9 g (94.0%)

$C_{15}H_{19}NO_3$ (261.3)

Calculated.	C 68.95	H 7.33	N 5.36
Found.	C 67.0	H 7.4	N 5.2

Example 14.



A) The penicillin was prepared as described in Example 2 from:

1) 6.0 g (0.0231 mol) of 4-(4-cycloheptene-1-carbonylamino)-benzoic acid, 2.69 ml (0.024 mol) of N-methylmorpholine and 2.3 ml (0.024 mol) of chloroformic acid ethyl ester.

2) 9.69 g (0.0277 mol) of ampicillin and 6.26 ml (0.0447 mol) of triethylamine.

Yield: 11.1 g (78.3%) of sodium D-α-[4-(4-cycloheptene-1-carbonylamino-benzoylamino)]-benzylpenicillin:

$C_{31}H_{33}N_4O_6SNa \cdot 2H_2O$ (648.7)

Calculated.	C 57.40	H 5.75	N 8.64	S 4.96
Found.	C 56.8	H 6.1	N 7.7	S 4.8

β-Lactam content: 77.2%

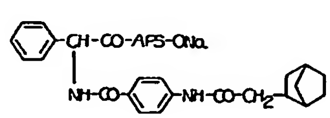
B) 4-(4-Cycloheptene-1-carbonylamino)-benzoic acid was prepared as described in Example 3 from 4.45 g (0.0324 mol) of *p*-aminobenzoic acid and 5.7 g (0.0359 mol) of 4-cycloheptene-1-carboxylic acid chloride.

Yield: 6.3 g (75%)

$C_{15}H_{17}NO_3$ (259.3)

Calculated.	C 69.48	H 6.61	N 5.40
Found.	C 67.8	H 6.5	N 4.8

Example 15.



A) The penicillin was prepared as described in Example 2 from:

1) 6.53 g (0.0239 mol) of 4-[bicyclo(2,2,1)hept-2-yl-acetamido]-benzoic acid, 2.78 ml (0.0248 mol) of N-methylmorpholine and 2.38 ml (0.0248 mol) of chloroformic acid ethyl ester.

2) 10.0 g (0.0286 mol) of ampicillin and 6.47 ml (0.0467 mol) of triethylamine.

Yield: 9.3 g (62%) of sodium D-α-[4-(2-norbornyl-acetamido-benzoylamino)]-benzylpenicillin:

$C_{32}H_{33}N_4O_6SNa \cdot 3H_2O$ (680.8)

Calculated.	C 56.56	H 6.07	N 8.23	S 4.72
Found.	C 54.9	H 5.9	N 8.7	S 5.7

β-Lactam content: 100%

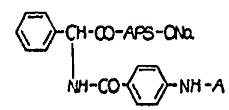
B) 4-[Bicyclo-(2,2,1)hept-2-yl-acetamido]-benzoic acid was prepared as described in Example 3 from 9.63 g (0.07 mol) of p-aminobenzoic acid and 13.2 g (0.077 mol) of bicyclo(2,2,1)hept-2-yl-acetyl chloride.

Yield: 17.4 g (91.2%)

$C_{16}H_{19}NO_3$ (273.3)

Calculated.	C 70.32	H 7.01	N 5.12
Found.	C 67.1	H 7.2	N 5.0

TABLE 3



The compounds of Examples 16 and 26 were prepared by the acid chloride method and that of Example 25 was prepared via the activated ester 4-benzoylamino-benzoic acid 1-hydroxybenzotriazole ester. All other examples were synthesised by the mixed anhydride method.

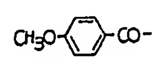
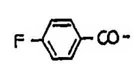
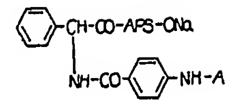
Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
16							
A) $C_{31}H_{29}N_4O_7SNa$		71.4	66.3	57.94	4.86	8.72	4.99
1 H_2O (642.7)				58.2	5.7	8.4	4.9
B) $C_{15}H_{13}NO_4$ (271.3)	4-(4-methoxybenzoyl-amino)-benzoic acid			66.41	4.83	5.16	
		84.5		65.5	4.8	5.0	
17							
A) $C_{30}H_{26}FN_4O_6SNa$				55.56	4.66	8.62	4.95
2 H_2O (648.6)		66.6	100	55.3	5.6	8.6	5.6
B) $C_{14}H_{10}FNO_3$	4-(4-fluorobenzoylamino)-Benzoic acid			64.88	3.89	5.41	
(259.2)		82.2		61.1	3.8	5.2	

TABLE 3 (continued)



The compounds of Examples 16 and 26 were prepared by the acid chloride method and that of Example 25 was prepared via the activated ester 4-benzoylamino-benzoic acid 1-hydroxybenzotriazole ester. All other examples were synthesised by the mixed anhydride method.

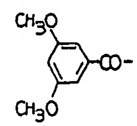
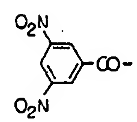
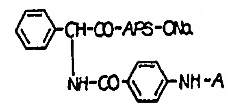
Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S	Cl
18								
A) $C_{32}H_{31}N_4O_8SN1$		76.2	100	55.64	5.11	8.11	4.65	
2 H_2O (690.7)				54.1	5.2	7.6	5.2	
B) $C_{16}H_{15}NO_5$ (301.3)	4-(3,5-dimethoxybenzoylamino)-benzoic acid			63.79	5.02	4.65		
		100		63.5	5.4	3.8		
19								
A) $C_{30}H_{25}N_6O_{10}SNa$		80.6	100	51.29	3.88	11.97	4.57	
1 H_2O (702.6)				51.2	4.7	10.5	4.6	
B) $C_{14}H_9N_3O_7$ (331.2)	4-(3,5-dinitrobenzoylamino)-benzoic acid			50.77	2.74	12.68		
		50.0		51.7	4.0	13.2		

TABLE 3 (continued)



The compounds of Examples 16 and 26 were prepared by the acid chloride method and that of Example 25 was prepared via the activated ester 4-benzoylamino-benzoic acid 1-hydroxybenzotriazole ester. All other examples were synthesised by the mixed anhydride method.

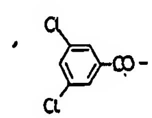
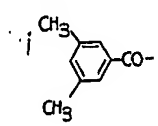
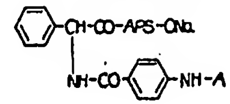
Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S	Cl
20								
A) $C_{30}H_{25}Cl_2N_4O_6SNa$		73.4	75.2	51.51	4.18	8.01	4.95	10.13
2 H_2O (699.549)				50.6	4.2	7.5	4.4	9.6
B) $C_{14}H_9Cl_2NO_3$ (310.1)	4-(3,5-dichlorobenzoylamino)-benzoic acid			54.23	2.93	4.52		22.86
		64		53.1	2.9	3.9		23.1
21								
A) $C_{32}H_{31}N_4O_6SNa$		74	96.7	58.35	5.51	8.50	4.88	
$2H_2O$ (658.7)				57.9	6.1	8.0	5.2	
B) $C_{16}H_{15}NO_3$ (255.3)	4-(3,5-dimethylbenzoylamino)-benzoic acid			71.36	5.61	5.20		
		91.8		68.8	5.6	4.3		

TABLE 3 (continued)



The compounds of Examples 16 and 26 were prepared by the acid chloride method and that of Example 25 was prepared via the activated ester 4-benzoylamino-benzoic acid 1-hydroxybenzotriazole ester. All other examples were synthesised by the mixed anhydride method.

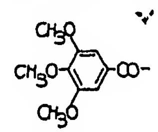
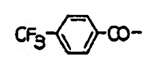
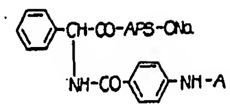
Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
22							
A) $C_{33}H_{33}N_4O_9SNa$		88.3	72.9	54.99	5.18	7.78	4.45
2 H_2O (720.7)				54.1	6.0	7.5	4.5
B) $C_{17}H_{17}NO_6$ (331.3)	4-(3,4,5-trimethoxybenzoylamino)-benzoic acid			61.63	5.17	4.23	
		94.6		61.8	5.2	3.9	
23							
A) $C_{31}H_{26}F_3N_4O_6SNa$		47.8	84.3	53.29	4.33	8.02	4.60
				52.6	5.6	7.7	5.7
2 H_2O (698.7)	4-(4-trifluoromethylbenzoylamino)-benzoic acid			58.25	3.26	4.53	
B) $C_{15}H_{10}F_3NO_3$ (309.2)		58.0		58.2	3.6	4.2	

TABLE 3 (continued)



The compounds of Examples 16 and 26 were prepared by the acid chloride method and that of Example 25 was prepared via the activated ester 4-benzoylamino-benzoic acid 1-hydroxybenzotriazole ester. All other examples were synthesised by the mixed anhydride method.

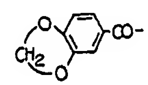
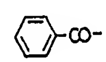
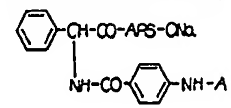
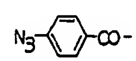
Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
24							
A) $C_{31}H_{27}N_4O_8SNa$		45.5	65.0	55.18	4.63	8.30	4.76
2 H_2O (674.7)				54.4	5.1	8.1	5.3
B) $C_{15}H_{11}NO_5$ (285.3)	4- 3,4-(methylenedioxy)-benzoylamino-benzoic acid			63.15	3.89	4.91	
		89		62.5	4.0	4.6	
25							
A) $C_{30}H_{27}N_4O_6SNa$		71.4	72.2	57.12	4.95	8.89	5.09
2 H_2O (630.7)				56.3	5.6	9.4	4.3
B) $C_{20}H_{14}N_4O_3$ (358.4)	4-benzoylamino-benzoic acid 1-hydroxy-benzotriazole ester			67.02	5.63	15.65	
		84		67.0	4.2	15.8	

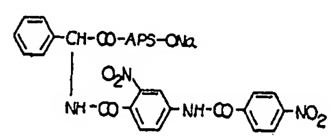
TABLE 3 (continued)



The compounds of Examples 16 and 26 were prepared by the acid chloride method and that of Example 25 was prepared via the activated ester 4-benzoylamino-benzoic acid 1-hydroxybenzotriazole ester. All other examples were synthesised by the mixed anhydride method.

Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
26							
A) $C_{30}H_{26}N_7O_6SNa$		81.8	90.5	53.64	4.50	14.60	4.78
2 H_2O (635.6)				53.0	4.8	14.8	4.8
B) $C_{14}H_{10}N_4O_3$ (282.3)	4-(4-azidobenzoylamino)-benzoic acid			59.57	3.58	19.85	
		83.9		59.6	3.4	20.4	

Example 27.



A) The above compound was prepared as described in Example 2 from:

1) 11.05 g (0.033 mol) of 4-(4-nitrobenzoylamino)-2-nitrobenzoic acid, 3.8 ml (0.034 mol) of N-methylmorpholine and 3.26 ml (0.034 mol) of chloroformic acid ethyl ester.

2) 14.0 g (0.04 mol) of ampicillin and 8.95 ml (0.064 mol) of triethylamine.

Yield: 8.3 g (36.6%) of sodium D-α-[4-(4-nitrobenzoylamino-2-nitrobenzoyl-amino)]-benzylpenicillin:

$C_{30}H_{25}N_6O_{10}SNa \cdot 2H_2O$ (720.6)

Calculated.	C 50.0	H 4.06	N 11.67	S 4.45
Found.	C 49.6	H 4.4	N 11.5	S 5.1

β-Lactam content: 86.0%

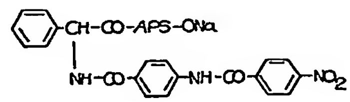
B) 4-(4-Nitrobenzoylamino)-2-nitrobenzoic acid was prepared as described in Example 3 from 20.0 g (0.11 mol) of 4-amino-2-nitrobenzoic acid and 22.4 g (0.121 mol) of 4-nitrobenzoyl chloride. The product was reprecipitated from THF/H_2O.

Yield: 29.9 g (82.2%)

$C_{14}H_9N_3O_7$ (331.2)

Calculated.	C 50.77	H 2.74	N 12.68
Found.	C 51.5	H 3.5	N 13.0

Example 28.



A) The above compound was prepared as described in Example 1 from: 15.0 g (0.0492 mol) of 4-(4-nitrobenzoylamino)-benzoyl chloride and 15.2 g (0.041 mol) of sodium ampicillin.

Yield: 20.5 g (78.5%) of sodium D-α-[4-(4-nitrobenzoylamino-benzoylamino)]-benzylpenicillin

$C_{30}H_{26}N_5O_8SNa \cdot 2H_2O$ (675.7)

Calculated.	C 53.32	H 4.47	N 10.37	S 4.75
Found.	C 53.3	H 4.4	N 11.0	S 5.4

β-Lactam content: 88.8%

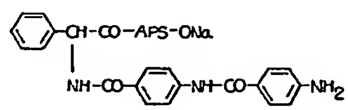
B) 4-(4-Nitrobenzoylamino)-benzoic acid was prepared as described in Example 3 from 15 g (0.11 mol) of PAB and 26.3 g (0.142 mol) of p-nitrobenzoyl chloride.

Yield: 30.1 g (96.2%)

$C_{14}H_{10}N_2O_5$ (286.2)

Calculated.	C 58.76	H 3.53	N 9.78
Found.	C 58.6	H 3.4	N 9.7

Example 29.



8.0 g (0.0125 mol) of sodium D-α-[4-(4-nitrobenzoylamino-benzoylamino)]-benzylpenicillin were dissolved in 250 ml of absolute methanol and hydrogenated, in the presence of hydrogen, using as catalyst 30 g of palladium black on 90 g calcium carbonate, for 60 minutes at 0° to 5°C. The catalyst was added to the reaction solution in 3 portions at intervals of 20 minutes during the hydrogenation. The catalyst was separated from the solvent and the filtrate was gently concentrated to dryness *in vacuo*. The residue was dissolved in a little methanol and the solution was treated with absolute ether. The resulting precipitate was filtered off and thoroughly dried.

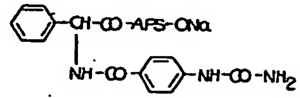
Yield: 7.0 g (91.9%) of sodium D-α-[4-(4-aminobenzoylamino-benzoylamino)]-benzylpenicillin:

$C_{30}H_{28}N_5O_6SNa \cdot 2H_2O$ (645.7)

Calculated.	C 55.81	H 5.00	N 10.85	S 4.97
Found.	C 54.7	H 5.7	N 10.4	S 5.2

β-Lactam content: 62.8%

Example 30.



A) The above compound was prepared as described in Example 2 from:

1) 6 g (0.0334 mol) of 4-carbamoylaminobenzoic acid, 3.74 ml (0.0334 mol) of N-methylmorpholine and 3.72 ml (0.0334 mol) of chloroformic acid ethyl ester.
2) 18.6 g (0.0533 mol) of ampicillin and 12 ml (0.0858 mol) of triethylamine.

Yield: 10.8 g (61.1%) of sodium D-α-(4-carbamoylamino-benzoylamino)-benzyl-penicillin:

$C_{24}H_{24}N_5O_6SNa \cdot 2H_2O$ (569.6)

Calculated.	C 50.61	H 4.95	N 12.29	S 5.64
Found.	C 50.7	H 5.1	N 10.7	S 5.9

β-Lactam content: 90.0%

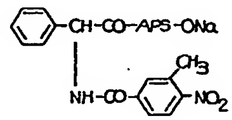
B) 4-Carbamoyl-aminobenzoic acid was prepared from 20 g (0.146 mol) of PAB and 12.5 g (0.154 mol) of potassium cyanate. The reaction solution was stirred at 80° until a clear solution was just produced. The solution was left to stand overnight at room temperature and was then acidified with 2 N HCl. The precipitate was filtered off and recrystallised from hot ethanol, with admixture of water.

Yield: 21.8 g (83%)

$C_8H_8N_2O_3$ (180.2)

Calculated.	C 53.32	H 4.48	N 15.54
Found.	C 53.0	H 4.6	N 15.2

Example 31.



The above compound was prepared as described in Example 1 from 12 g (0.0324 mol) of sodium ampicillin and 7.08 g (0.354 mol) of 4-nitro-3-methylbenzoyl chloride.

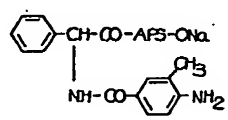
Yield: 12.6 g (73.1%) of sodium D-α-(4-nitro-3-methylbenzoylamino)-benzyl-penicillin:

$C_{24}H_{23}N_4O_7SNa \cdot 1H_2O$ (552.5)

Calculated.	C 52.17	H 4.56	N 10.14	S 5.81
Found.	C 52.0	H 5.0	N 9.8	S 5.9

β-Lactam content: 72.2%

Example 32.



The above compound was prepared as described in Example 29 by catalytic hydrogenation of 5 g (0.0094 mol) of sodium D-α-(4-nitro-3-methyl-benzoylamino)-benzyl-penicillin.

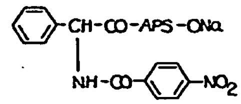
Yield: 4.1 g (87.0%) of sodium D-α-(4-amino-3-methylbenzoylamino)-benzyl-penicillin:

$C_{24}H_{25}N_4O_5SNa \cdot 2H_2O$ (540.6)

Calculated.	C 53.32	H 5.40	N 10.37	S 5.94
Found.	C 52.7	H 5.3	N 9.5	S 5.4

β-Lactam content: 71.9%

Example 33.



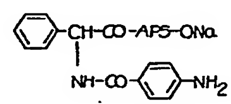
The above compound was prepared as described in Example 1 from 15 g (0.0403 mol) of sodium ampicillin and 9.75 g (0.0526 mol) of p-nitrobenzoyl chloride.

Yield: 19.2 g (91.5%) of sodium D-α-(4-nitro-benzoylamino)-benzylpenicillin: $C_{23}H_{21}N_4O_7SNa$. $1H_2O$ (538.5)

Calculated.	C 51.30	H 4.31	N 10.40	S 5.96
Found.	C 52.0	H 5.2	N 9.4	S 5.5

β-Lactam content: 76.8%

Example 34.



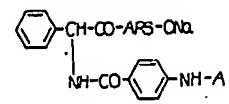
The above compound was prepared as described in Example 29 by catalytic hydrogenation of 8.0 g (0.0154 mol) of sodium D-α-(4-nitro-benzoylamino)-benzylpenicillin.

Yield: 6.0 g (79.8%) of sodium D-α-(4-amino-benzoylamino)-benzylpenicillin $C_{23}H_{23}N_4O_5SNa$. $1H_2O$ (508.5)

Calculated.	C 54.33	H 4.96	N 11.02	S 6.31
Found.	C 55.7	H 6.0	N 9.5	S 5.9

β-Lactam content: 68.7%

TABLE 4



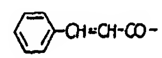
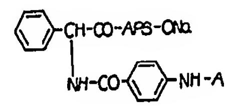
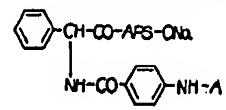
Example No. A) Composition (Molecular weight) and B) Starting substance	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
35 A) $C_{32}H_{29}N_4O_6SNa$ .3 H_2O (647.7)		80.4	95.2	56.97	5.23	8.30	4.75
				56.2	5.8	8.2	5.5
B) $C_{16}H_{13}NO_3$ (267.3)	4-cinnamoyl-aminobenzoic acid	97.4		71.90	4.90	5.24	
				71.6	4.7	4.7	
36 A) $C_{25}H_{24}N_7O_6SNa$ .1 H_2O (591.6)	N_3-CH_2-CO-	78.0	87.5	50.76	4.43	16.54	5.42
				50.6	4.7	16.6	5.4
B) $C_9H_8N_4O_3$ (220.2)	4-azidoacetyl-aminobenzoic acid	98.2		49.09	3.67	25.45	
				48.8	3.5	25.0	
37 A) $C_{26}H_{26}N_7O_6SNa$ .1 H_2O (587.6)	N_3(CH_3)CH-CO-	88.8	71.0	51.57	4.66	16.19	5.30
				51.6	5.6	15.3	4.9
B) $C_{10}H_{10}N_4O_3$ (234.2)	4-(2-azidopropionyl)-aminobenzoic acid	86.0		51.31	4.31	23.92	
				51.3	4.2	23.3	

TABLE 4 (continued)



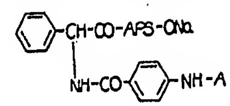
Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
38							
A) $C_{26}H_{26}N_7O_6SNa$ .2 H_2O (623.6)	N_3-CH_2-CH_2-CO-	81.0	96	50.08	4.85	15.72	5.15
				50.3	4.6	14.6	5.5
B) $C_{10}H_{10}N_4O_3$ (234.2)	4-azidopropionyl-aminobenzoic acid			51.29	4.31	23.92	
		89		51.3	4.2	22.5	
39							
A) $C_{28}H_{30}N_7O_6SNa$ .2 H_2O (651.7)	N_3–CH_2–C(CH_3)(CH_3)–CO–	76.7	94.8	51.60	5.26	15.05	4.92
				50.7	6.0	13.1	5.3
B) $C_{12}H_{14}N_4O_3$ (262.3)	4-(3-aziod-2,2-dimethyl-propionyl)-amino-benzoic acid			54.95	5.38	21.36	
		73.8		54.0	5.4	20.7	

TABLE 4 (continued)



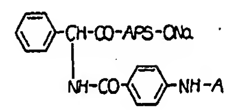
Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
40							
A) $C_{27}H_{28}N_7O_6SNa$	N_3 CH-CH_2-CO- CH_3	68.1	81.6	52.34	4.88	15.82	5.18
.1 H_2O (619.6)				52.2	5.3	13.1	5.8
B) $C_{11}H_{12}N_4O_3$ (248.2)	4-(3-azido-butyric acid amido)-benzoic acid			53.24	4.88	22.57	
		70.2		53.6	5.0	20.2	
41							
A) $C_{24}H_{23}N_4O_6SNa$	H-CO-	63.4	53.9	50.35	5.11	9.79	5.6
.3 H_2O (572.6)			88.3	50.0	5.6	8.4	5.5
B) $C_8H_7NO_3$ (165.15)	4-formyl-aminobenzoic acid			58.25	4.25	8.5	
		53.1		57.9	4.3	8.3	

TABLE 4 (continued)



Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
42 A) $C_{26}H_{27}N_4O_7SNa$ .2 H_2O (598.6)	CH_3O-CH_2-CO-	83.8	88	52.17	5.22	9.36	5.36
				52.9	5.4	9.0	5.4
B) $C_{10}H_{11}NO_4$ (209.2)	4-methoxyacetamido-benzoic acid			57.42	5.30	6.69	
		46.6		56.9	5.2	6.2	
43 $C_{24}H_{25}N_4O_6SNa$ .3 H_2O (558.6)	CH_3-	78.3	94.0	51.61	5.59	10.03	5.75
				51.4	5.7	9.4	6.3
44 A) $C_{25}H_{26}N_5O_6SNa$ .2H_2O (583.6)	CH_3-NH-CO-	67.2	87.3	51.46	5.18	11.99	5.50
				52.0	6.3	10.5	6.0

TABLE 4 (continued)



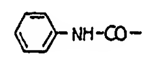
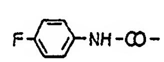
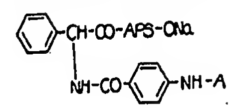
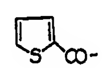
Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
45							
A) $C_{30}H_{28}N_5O_6SNa$ .2 H_2O		90.8	90.7	55.81	5.00	10.85	4.97
(609.6)				55.9	5.9	10.3	5.6
B) $C_{14}H_{12}N_2O_3$ (256.4)	p-phenylureido-benzoic acid			65.59	4.72	10.92	
		78.8		66.1	4.6	10.9	
46							
A) $C_{30}H_{27}FN_5O_6SNa$ .2 H_2O		82.5	89.8	54.30	4.71	10.55	4.84
(663.7)				54.5	5.3	9.5	4.7
B) $C_{14}H_{11}FN_2O_3$ (274.3)	4-(4-fluorophenylureido)-benzoic acid			61.30	4.04	10.21	
		88		60.7	4.1	10.0	

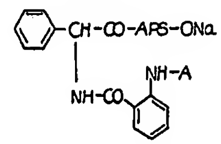
TABLE 4 (continued)

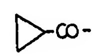
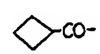


Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
47							
A) $C_{25}H_{26}N_5O_5S_2Na\ .2\ H_2O$ (599.7)	CH_3-NH-CS-	70.6	86.8	50.07	5.04	11.68	10.71
				50.6	5.1	10.9	9.3
B) $C_9H_{10}N_2O_2S$ (210.3)	4-methylthioureido-benzoic acid			51.41	4.79	13.32	15.25
				51.7	5.0	13.3	14.6
48							
A) $C_{28}H_{25}N_4O_6S_2Na\ .2\ H_2O$ (636.7)		68.5	88.1	52.82	4.59	8.81	10.08
				52.3	4.6	8.9	10.2
B) $C_{12}H_9NO_3S$ (247.3)	4-(thiophene-2-carbonylamino)- benzoic acid			58.28	3.67	5.66	12.96
		69.8		57.6	3.7	5.5	12.8

Notes: Examples 35, 39, 40, 41, 42, 43, 46, 47 and 48 used the mixed anhydride method (as described in Example 2) and Examples 36, 37, 38, 44 and 45 the acid chloride process.

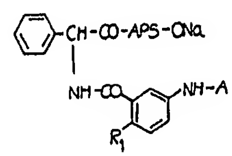
TABLE 5



Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
49							
A) $C_{27}H_{27}N_4O_6SNa$.$2H_2O$		50.5	69.1	54.54	5.25	9.42	5.40
(594.6)				52.9	6.3	8.0	6.2
B) $C_{11}H_{11}NO_3$ (205.2)	2-cyclopropanecarbonylamino-benzoic acid			64.39	5.40	6.82	
		54.7		63.7	5.2	7.4	
50							
A) $C_{28}H_{29}N_4O_6SNa$.$2H_2O$		41.7	85.3	55.26	5.46	9.2	5.28
(608.6)				54.7	5.6	8.7	5.7
B) $C_{12}H_{13}NO_3$ (219.2)	2-cyclobutanecarbonylamino-benzoic acid			65.75	5.98	6.39	
		69.7		65.3	6.0	6.3	

The compounds of Examples 49 and 50 were prepared according to the mixed anhydride method.

TABLE 6



(Method of synthesis: as described in Example 2)

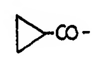
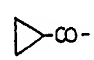
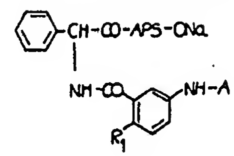
Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S	Cl
51								
A) $C_{27}H_{27}N_4O_6SNa \cdot 2H_2O$		86.7	81.9	54.54	5.25	9.42	5.40	
(594.6)	R_1 : H			54.6	6.2	9.6	6.4	
B) $C_{11}H_{11}NO_3$ (205.216)	3-cyclopropanecarbonylamino-benzoic acid			64.39	5.40	6.82		
		89.8		63.8	5.6	6.9		
52								
A) $C_{28}H_{28}ClN_4O_6SNa \cdot 2H_2O$		78.6	88.7	52.29	5.02	8.71	4.99	5.51
(643.1)	R_1 : Cl			53.1	5.5	8.0	4.8	5.2
B) $C_{12}H_{12}ClNO_3$ (253.7)	3-cyclobutanecarbonylamino-6-chloro-benzoic acid			56.82	4.77	5.52		13.97
		70		56.3	4.8	5.3		14.0

TABLE 6 (continued)



(Method of synthesis: as described in Example 2)

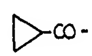
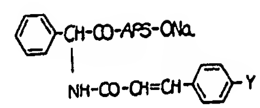
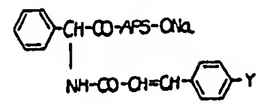
Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found: C	H	N	S	Cl
53 A) $C_{27}H_{26}ClN_4O_6SNa$ .1 H_2O (611.0)	 R_1 : Cl	82.5	88.8	53.08	4.62	9.17	5.25	5.80
				52.8	5.6	8.1	5.4	5.1
B) $C_{11}H_{10}ClNO_3$ (239.7)	3-cyclopropanecarbonylamino-6-chlorobenzoic acid			55.12	4.21	5.85		14.79
		75.7		55.0	4.3	5.8		14.4

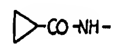
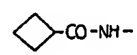
TABLE 7



Example No. A) Composition (Molecular weight) and B) Starting compound	Y	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
54 $C_{25}H_{23}N_4O_7SNa$.$2H_2O$ (582.6)	NO_2-	82.4	82.5	51.54 52.9	4.67 5.6	9.62 9.1	5.51 5.6
55 A) $C_{26}H_{25}N_4O_6SNa$.$2H_2O$ (580.6)	H-CO-NH-	76.5	91.8	53.79 53.8	5.03 5.4	9.65 9.4	5.53 5.5
B) $C_{10}H_9NO_3$ (191.2)	4-formyl-aminocinnamic acid	34.9		62.82 62.9	4.74 4.8	7.32 7.4	

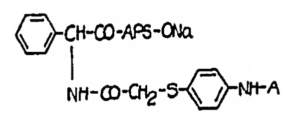
TABLE 7 (continued)



Example No. A) Composition (Molecular weight) and B) Starting compound	Y	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
56							
A) $C_{29}H_{29}N_4O_6SNa$ .2 H_2O (620.7)		80.5	77.9	56.12	5.36	9.01	5.17
				56.0	5.5	8.9	5.3
B) $C_{13}H_{13}NO_3$ (231.3)	4-cyclopropanecarbonylamino-cinnamic acid			67.54	5.66	6.05	
		68.4		66.9	5.8	6.0	
57							
A) $C_{30}H_{31}N_4O_6SNa$ .2 H_2O (634.7)		78.2	83.7	56.78	5.56	8.83	5.06
				57.5	5.5	9.3	5.3
B) $C_{14}H_{15}NO_3$ (245.3)	4-cyclobutanecarbonylaminocinnamic-acid			68.56	6.16	5.71	
		81.0		67.9	6.3	5.6	

Notes: The compound of Example 54 was prepared via the acid chloride method and those of Examples 55, 56 and 57 were prepared via the mixed anhydride method.

TABLE 8



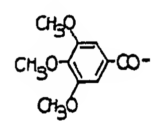
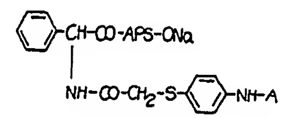
Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
58							
A) $C_{34}H_{35}N_4O_9S_2Na$		97	96.8	53.25	5.13	7.31	8.37
.2 H_2O (766.8)				54.0	5.5	6.9	8.4
B) $C_{18}H_{19}NO_6S$ (377.4)	[4-(3,4,5-trimethoxybenzoylamino-phenylthio)]-acetic acid			57.29	5.08	3.72	8.50
		82.5		56.1	5.0	3.3	8.0
59							
A) $C_{25}H_{25}N_4O_6S_2Na$	H-CO-	75.5	100	51.54	4.67	9.62	11.00
.1 H_2O (582.6)				51.9	5.1	8.7	10.5
B) $C_9H_9NO_3S$ (211.2)	(p-formylamino-phenylthio)-acetic acid			51.18	4.30	6.63	15.18
		50.5		50.9	4.4	6.7	14.9

TABLE 8 (continued)



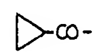
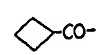
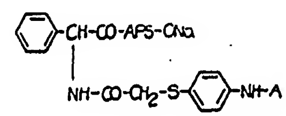
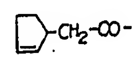
Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
60							
A) $C_{28}H_{29}N_4O_6S_2Na$ .1 H_2O (622.7)		87.5	81.5	54.01	5.02	9.00	10.23
				54.0	5.7	8.5	10.2
B) $C_{12}H_{13}NO_3S$ (251.3)	(p-cyclopropanecarbonylaminophenyl-thio)-acetic acid			57.35	5.21	5.57	12.75
		76.9		56.5	5.0	5.6	12.8
61							
A) $C_{29}H_{31}N_4O_6S_2Na$ .1 H_2O (636.7)		73.8	98.5	54.71	5.22	8.80	10.08
				54.7	5.6	8.7	10.1
B) $C_{13}H_{15}NO_3S$ (265.3)	(p-cyclobutanecarbonylamino-phenylthio)-acetic acid			58.85	5.70	5.28	12.08
		58.6		58.9	5.7	4.6	11.09

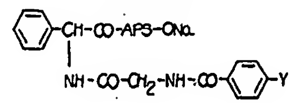
TABLE 8 (continued)



Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
62							
A) $C_{31}H_{33}N_4O_6SNa$		52.3	91.1	56.18	5.32	8.45	9.69
.1 H_2O (662.8)				56.6	5.6	8.0	9.6
B) $C_{15}H_{17}NO_3S$ (291.4)	[p-(2-cyclopentene-1-acetyl)-amino-phenylthio]-acetic acid			61.83	5.88	4.81	11.00
		69.5		61.0	5.4	4.5	11.0

Note: All 5 Examples used the mixed anhydride method.

TABLE 9



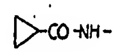
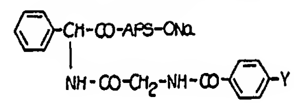
Example No. A) Composition (Molecular weight) and B) Starting compound	Y	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
63							
A) $C_{26}H_{26}N_5O_7SNa$	H-CO-NH-	66.9	91.5	51.06	4.94	11.45	5.25
.2 H_2O (611.6)				52.0	4.7	11.0	6.2
B) $C_{10}H_{10}N_2O_4$ (222.2)	N-(p-formylaminobenzoyl)-glycine			54.05	4.54	12.55	
		45.3		53.7	4.8	12.4	
64							
A) $C_{29}H_{30}N_5O_7SNa$		74.0	78.1	54.97	5.08	11.05	5.07
.1 H_2O (633.7)				55.5	6.6	9.7	4.5
B) $C_{13}H_{14}N_2O_4$ (262.3)	N-(p-cyclopropanecarbonylamino-benzoyl)-glycine			59.53	5.38	10.68	
		67.4		59.2	5.4	10.5	

TABLE 9 (continued)



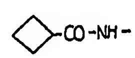
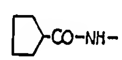
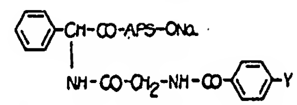
Example No. A) Composition (Molecular weight) and B) Starting compound	Y	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
65							
A) $C_{30}H_{32}N_5O_7SNa$		58.6	70.2	54.23	5.45	10.52	4.82
.2 H_2O (665.7)				54.8	5.9	10.1	4.7
B) $C_{14}H_{16}N_2O_4$ (276.3)	N-(p-cyclobutanecarbonylamino-benzoyl)-glycine			60.86	5.83	10.14	
		68.4		61.1	5.8	10.3	
66							
A) $C_{31}H_{34}N_5O_7SNa$		96.1	89.2	54.78	5.63	10.30	4.73
.2 H_2O (679.7)				54.2	5.6	10.4	5.0
B) $C_{15}H_{18}N_2O_4$ (290.3)	N-(p-cyclopentanecarbonylamino-benzoyl)-glycine			62.06	6.25	9.65	
		65.1		61.4	5.9	9.4	

TABLE 9 (continued)



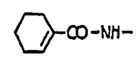
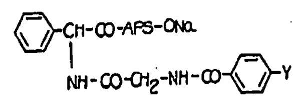
Example No. A) Composition (Molecular weight) and B) Starting compound	Y	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
67							
A) $C_{32}H_{34}N_8O_7SNa$ .1 H_2O (673.7)		78.5	93.5	57.05	5.38	10.40	4.77
				56.6	6.5	9.8	4.8
B) $C_{16}H_{18}N_2O_4$ (302.3)	N-[p-(1-cyclohexene-1-carbonyl)-aminobenzoyl]-glycine			63.58	6.00	9.27	
		61.7		62.8	5.7	8.8	
68							
A) $C_{25}H_{24}N_7O_6SNa$ .1 H_2O (591.6)	N_3-	89.8	88.1	50.76	4.30	16.08	5.27
				51.6	5.1	15.6	5.2
B) $C_9H_8N_4O_3$ (220.2)	N-(p-azidobenzoyl)-glycine			49.09	3.67	25.45	
		31.8		49.1	3.7	25.4	

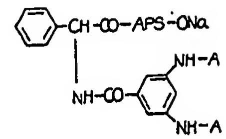
TABLE 9 (continued)



Example No. A) Composition (Molecular weight) and B) Starting compound	Y	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
69 A) $C_{25}H_{24}N_5O_8SNa$ .1 H_2O (595.6)	NO_2-	74.3	77	50.42	4.40	11.76	5.39
				50.0	4.9	11.5	5.5
B) $C_9H_8N_2O_5$ (224.2)	N-(p-nitrobenzoyl)-glycine			48.22	3.6	12.50	
		56.2		48.2	3.5	11.7	
70 $C_{25}H_{26}N_5O_6SNa$ .2 H_2O (583.6)	NH_2-	93.0	58.7	51.46	5.18	12.00	5.50
				51.5	5.4	10.9	5.5

Notes: Examples 63 to 69 used the mixed anhydride synthesis. Example 70 used catalytic hydrogenation (as described in Example 29) of the compound of Example 69.

TABLE 10



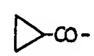
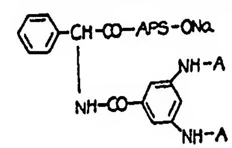
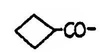
Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
71 A) $C_{25}H_{24}N_5O_7SNa$ .1 H_2O (579.6)	H-CO-	75.4	90.3	51.81	4.53	12.08	5.54
				51.6	4.9	11.5	5.5
B) $C_9H_8N_2O_4$ (208.2)	3,5-bis-formylamino-benzoic acid			51.92	3.88	13.46	
		86		51.1	3.9	13.0	
72 A) $C_{31}H_{32}N_5O_7SNa$ .2 H_2O (677.7)		66.7	87.5	54.94	5.35	10.33	4.74
				54.8	5.7	8.8	5.4
B) $C_{15}H_{16}N_2O_4$ (288.3)	3,5-bis-(cyclopropanecarbonyl-amino) benzoic acid			62.49	5.59	9.72	
		77.0		61.5	6.5	8.0	

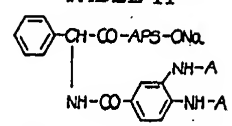
TABLE 10 (continued)

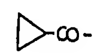


Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
73							
A) $C_{33}H_{36}N_5O_7SNa$		71.5	94.7	56.16	5.72	9.93	4.55
$.2\ H_2O$ (705.8)				55.4	5.7	8.6	5.3
B) $C_{17}H_{20}N_2O_4$ (316.4)	3,5-bis-(cyclobutanecarbonyl-amino)-benzoic acid			64.54	6.37	8.86	
		97.0		63.0	6.4	7.7	

All three compounds (71-73) were prepared via the mixed anhydride method.

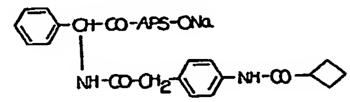
TABLE 11



Example No. A) Composition (Molecular weight) and B) Starting compound	A	Yield %	β-Lactam content %	Analysis, % calculated / found C	H	N	S
74							
A) $C_{25}H_{24}N_5O_7SNa$ .2 H_2O (597.6)	H-CO-	45.4	100	50.25	4.72	11.72	5.37
				49.5	4.0	9.6	6.8
B) $C_9H_8N_2O_4$ (208.2)	3,4-bis-formylamino-benzoic acid			51.92	3.88	13.46	
		79.6		50.7	3.8	12.8	
75							
A) $C_{31}H_{32}N_5O_7SNa$ .2 H_2O (677.7)		71.8	100	54.94	5.35	9.33	4.74
				54.1	5.4	9.5	5.2
B) $C_{15}H_{16}N_2O_4$ (288.3)	3,4-bis-(cyclopropanecarbonyl-amino) benzoic acid			62.49	5.59	9.72	
		41.4		61.1	5.7	10.1	

Both compounds (74 and 75) were prepared via the mixed anhydride method.

Example 76.



A) The above compound was prepared as described in Example 2 from:

1) 5.78 g (0.0248 mol) of (4-cyclobutanecarbonylaminophenyl)-acetic acid, 2.8 ml (0.025 mol) of N-methylmorpholine and 2.4 ml (0.025 mol) of chloroformic acid ethyl ester.
2) 10.4 g (0.0298 mol) of ampicillin and 6.68 ml (0.0477 mol) of triethylamine.

Yield: 13.1 g (90.3%) sodium D-α-[(4-cyclobutanecarbonylaminophenyl)-acetamido]-benzylpenicillin:

$C_{29}H_{31}N_4O_6SNa \cdot 2H_2O$ (622.7)

Calculated.	C 55.95	H 5.66	N 9.00	S 5.15
Found.	C 56.5	H 5.8	N 9.7	S 5.5

β-Lactam content: 87.8%

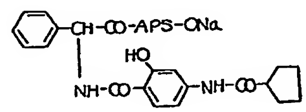
B) (4-Cyclobutanecarbonylaminophenyl)-acetic acid was prepared as described in Example 3 from 7.0 g (0.0464 mol) of p-aminophenyl)-acetic acid and 6.6 g (0.0557 mol) of cyclobutanecarboxylic acid chloride.

Yield: 10.0 g (83.3%)

$C_{13}H_{15}NO_3$ (233.3)

Calculated.	C 66.93	H 6.48	N 6.00
Found.	C 66.5	H 6.3	N 5.7

Example 77.



A) The above compound was prepared similarly to that of Example 26 via the N-hydroxy-benzotriazole method [W. König and R. Geiger, Chem. Ber. *103*, 788—798 (1970)] from the following components:

1) 4.7 g (0.0188 mol) of 4-cyclopentanecarbonylamino-2-hydroxybenzoic acid, 2.69 g (0.0198 mol) of 1-hydroxybenzotriazole and 4.17 g (0.0202 mol) of dicyclohexylcarbodiimide (DCC).
2) 7.86 g (0.0225 mol) of ampicillin and 5.53 ml (0.0394 mol) of triethylamine.

Yield: 8.4 g (74.0%) of sodium D-α-(4-cyclopentanecarbonylamino-2-hydroxybenzoylamino)-benzylpenicillin:

$C_{29}H_{31}N_4O_7SNa \cdot 2H_2O$ (638.7)

Calculated.	C 54.54	H 5.52	N 8.77	S 5.03
Found.	C 54.3	H 5.8	N 9.6	S 4.8

β-Lactam content: 73.8%.

Activity against *E. coli* 14:	2— 4 U/ml
Activity against *Proteus vulg.* 1017:	8—16 U/ml
Activity against *Psdm. aerug.* Walter:	8—16 U/ml
Activity against *Klebs.* 63:	32—64 U/ml
Activity against *Staph. aureus* 1756:	32—64 U/ml

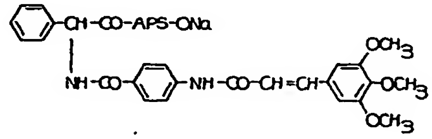
B) 4-Cyclopentanecarbonylamino-2-hydroxy-benzoic acid was prepared as described in Example 3 from 8 g (0.0379 mol) of 4-amino-2-hydroxy-benzoic acid (sodium salt, with 2 mols of H_2O) and 5.28 g (0.0398 mol) of cyclopentane carboxylic acid chloride.

Yield: 7.2 g (76.3%)

$C_{13}H_{15}NO_4$ (249.3)

Calculated.	C 62.63	H 6.06	N 5.62
Found.	C 62.7	H 6.3	N 5.5

Example 78.



A) The penicillin was prepared as described in Example 2 from:
1) 5.6 g (0.0157 mol) of 4-(3,4,5-trimethoxycinnamoylamino)-benzoic acid, 1.83 ml (0.0163 mol) of N-methylmorpholine and 1.57 ml (0.0163 mol) of chloroformic acid ethyl ester.
2) 6.58 g (0.0188 mol) of ampicillin and 4.26 ml (0.0304 mol) of triethylamine.

Yield: 9.3 g (83.4%) of sodium D-α-[4-(3,4,5-trimethoxycinnamoylamino-benzoylamino)]-benzylpenicillin:

$C_{35}H_{35}N_4O_9SNa$. $2H_2O$ (746.8)

Calculated.	C 56.29	H 5.27	N 7.51	S 4.30
Found.	C 54.9	H 5.7	N 6.8	S 4.7

β-Lactam content: 90.2%

Activity against *E. coli* 14:	2—4 U/ml
Activity against *Proteus vulg.* 1017:	128—256 U/ml
Activity against *Psdm. aerug.* Walter:	32—64 U/ml
Activity against *Klebs.* 63:	32—64 U/ml

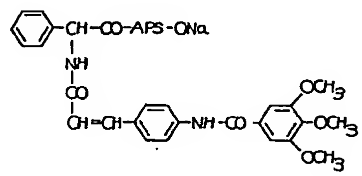
B) 4-(3,4,5-trimethoxycinnamoylamino)-benzoic acid was prepared as described in Example 3 from 3.3 g (0.0241 mol) of PAB and 6.8 g (0.0265 mol) of 3,4,5-trimethoxycinnamoyl chloride.

Yield: 5.6 g (65.1%), recrystallisation from THF/n-pentane

$C_{19}H_{19}NO_6$ (357.4)

Calculated.	C 63.85	H 5.35	N 3.91
Found.	C 62.5	H 5.4	N 3.3

Example 79.



A) The above compound was prepared as described in Example 2 from:
1) 6.1 g (0.0171 mol) of 4-(3,4,5-trimethoxy benzoylamino)-cinnamic acid, 1.98 ml (0.0177 mol) of N-methylmorpholine and 1.7 ml (0.0177 mol) of chloroformic acid ethyl ester.
2) 7.14 g (0.0204 mol) of ampicillin and 4.62 ml (0.033 mol) of triethylamine.

Yield: 10.3 g (85%) of sodium D-α-[4-(3,4,5-trimethoxybenzoylamino-cinnamoylamino)]-benzylpenicillin:

$C_{35}H_{35}N_4O_9SNa$. $2H_2O$ (746.8)

Calculated.	C 56.29	H 5.27	N 7.51	S 4.30
Found.	C 56.0	H 6.0	N 7.0	S 4.5

β-Lactam content: 89.7%

Activity against *E. coli* 14:	1—2 U/ml
Activity against *Proteus vulg.* 1017:	128—256 U/ml
Activity against *Psdm. aerug.* F. 41:	8—16 U/ml
Activity against *Klebs.* 63:	32—64 U/ml
Activity against *Staph. aureus* 133:	<1 U/ml

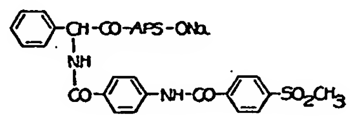
B) 4-(3,4,5-Trimethoxybensoylamino)-cinnamic acid was prepared as described in Example 3 from 5 g (0.0271 mol) of p-aminocinnamic acid hydrochloride and 3,4,5-trimethoxybenzoyl chloride.

Yield: 6.8 g (70.2%)

$C_{19}H_{19}NO_6$ (357.4)

Calculated.	C 63.85	H 5.35	N 3.91
Found.	C 63.6	H 5.4	N 3.2

Example 80.



A) The above compound was prepared as described in Example 2 from:

1) 3.6 g (0.0113 mol) of 4-(p-methylsulphonyl-benzoylamino)-benzoic acid, 1.4 ml (0.0125 mol) of N-methylmorpholine and 1.2 ml (0.0125 mol) of chloroformic acid ethyl ester.

2) 4.75 g (0.0136 mol) of ampicillin and 3.05 ml (0.0218 mol) of triethylamine.

Yield: 5.6 g (70%) of sodium D-α-[4-(p-methylsulphonylbenzoylamino-benzoyl-amino)]-benzylpenicillin:

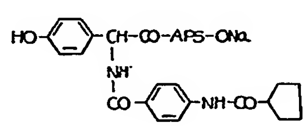
$C_{31}H_{29}N_4O_8S_2Na \cdot 2H_2O$ (708.7)

Calculated.	C 52.53	H 4.70	N 7.92	S 9.06
Found.	C 52.1	H 5.1	N 6.3	S 8.9

β-Lactam content: 72.9%

Activity against *E. coli* 14:	4—8 U/ml
Activity against *Proteus vulg.* 1017:	128—256 U/ml
Activity against *Psdm. aerug.* F 41:	32—64 U/ml
Activity against *Klebs.* 63:	32—64 U/ml
Activity against *Staph. aureus* 133:	<1 U/ml

Example 81.



A) The above compound was prepared as described in Example 1 from:

7.0 g (0.0168 mol) of p-hydroxyampicillin [D-6-(α-amino-p-hydroxyphenylacetyl-amino)-penicillin] and 5.5 g (0.0219 mol) of 4-cyclopentanecarbonylamino-benzoyl chloride (see Example 7C).

Yield: 5.9 (51.8%) of sodium D-α-[4-cyclopentanecarbonylamino-benzoylamino]-(p-hydroxybenzyl)-penicillin:

$C_{29}H_{31}N_4O_7SNa \cdot 3H_2O$ (656.7)

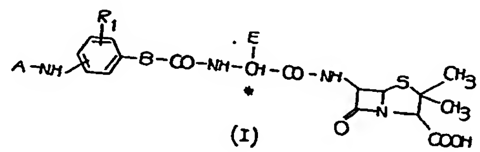
Calculated.	C 53.04	H 5.68	N 8.53	S 4.89
Found.	C 52.3	H 5.8	N 8.4	S 6.6

β-Lactam content: 79.6%

Activity against *E. coli* 14:	4—8 U/ml
Activity against *Proteus vulg.* 1017:	>256 U/ml
Activity against *Psdm. aerug.* F 41:	32—64 U/ml
Activity against *Klebs.* 63:	128—256 U/ml
Activity against *Staph. aureus* 133:	<1 U/ml

WHAT WE CLAIM IS:—

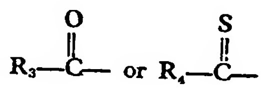
1. Compounds which are penicillins of the following general formula and their salts:



(I)

in which:

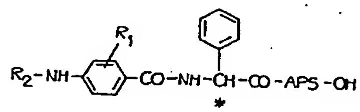
R_1 is a hydrogen, halogen, lower alkyl, hydroxyl, —NH—A or nitro radical;
A is a radical R_2 or



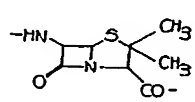
[in which:

R_2 is a hydrogen, lower alkyl or phenylsulphenyl radical;
R_3 is a hydrogen, lower alkyl, halo-(lower alkyl), cycloalkyl or cycloalkenyl radical with up to 11 carbon atoms, a bicycloalkyl or bicycloalkenyl radical with up to 8 carbon atoms, a phenyl radical carrying at least one substituent, or an azidoalkyl, amino, cinnamoyl, or heterocyclyl radical;
R_4 is a lower alkylamino, phenylamino or (substituted-phenyl)-amino radical];
B is a single bond or a group $—CH_2—$, $—S—CH_2—$, $—CH=CH—$ or $—CO—NH—CH_2—$;
E is a phenyl radical or a hydroxy-, azido-, lower alkyl-, lower alkoxy-, lower alkylthio- or chlorine-substituted phenyl, or thenyl radical; and
C* is an asymmetric carbon atom.

2. Penicillins according to Claim 1, of the general formula:



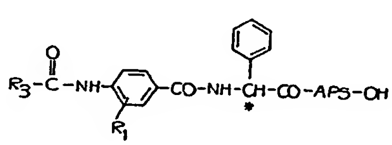
in which
—APS— is an aminopenicillanic acid residue of the formula:



; and

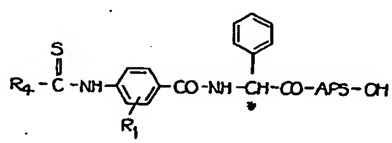
R_1 is a hydrogen, nitro or halogen radical;
R_2 is a hydrogen, lower alkyl or arylsulphenyl radical and their pharmaceutically acceptable salts.

3. Penicillins according to claim 1, of the general formula:



in which
—APS— is as defined in claim 2, R_3 is as defined in claim 1, and their pharmaceutically acceptable salts.

4. Penicillins according to claim 1, of the general formula:



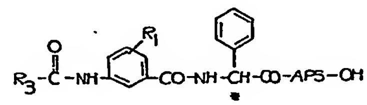
in which

—APS— is as defined in claim 2; and

R_1 is a hydrogen, nitro or halogen radical; and their pharmaceutically acceptable salts.

R_3 is a lower alkylamino, arylamino or (substituted aryl)-amino radical.

5. Penicillins according to Claim 1, of the general formula:—



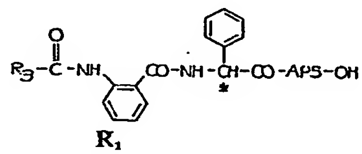
in which

—APS— is as defined in claim 2;

R_1 is a hydrogen or halogen radical; and

R_3 is a hydrogen, lower alkyl or cycloalkyl radical, or a cycloalkenyl radical with up to 11 carbon atoms; and their pharmaceutically acceptable salts.

6. Penicillins according to Claim 1, of the general formula:—

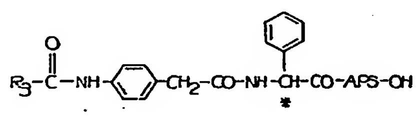


in which

—APA— is as defined in claim 2; and

R_3 is a hydrogen or lower alkyl radical, or a cycloalkyl or cycloalkenyl radical with up to 11 carbon atoms; and their pharmaceutically acceptable salts.

7. Penicillins according to Claim 1, of the general formula:—

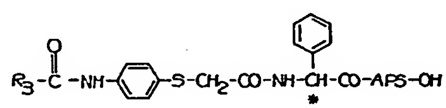


in which

—APS— is as defined in claim 2,

R_3 is as defined in claim 1, and their pharmaceutically acceptable salts.

8. Penicillins according to Claim 1, of the general formula:—

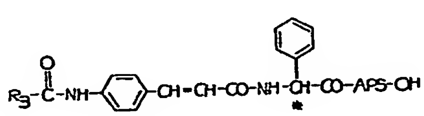


in which

—APS— is as defined in claim 2,

R_3 is as defined in claim 1 and their pharmaceutically acceptable salts.

9. Penicillins according to Claim 1, of the general formula:—

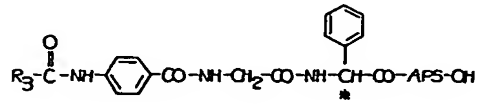


in which

—APS— is as defined in claim 2,

R_3 is as defined in claim 1, and their pharmaceutically acceptable salts.

10. Penicillins according to Claim 1, of the general formula:—

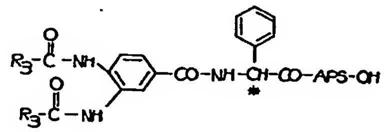


in which

—APS— is as defined in claim 2,

R_3 is as defined in claim 1, and their pharmaceutically acceptable salts.

11. Penicillins according to claim 1, of the general formula:—

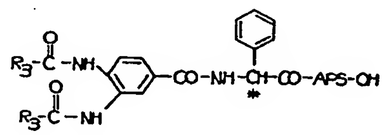


in which

—APS— is as defined in claim 2; and

R_3 is a hydrogen or lower alkyl radical, or a cycloalkyl or cycloalkenyl radical with up to 11 carbon atoms.

12. Penicillins according to Claim 1, of the general formula:—



in which

—APS— is as defined in claim 2; and

R_3 is a hydrogen or lower alkyl radical, or a cycloalkyl or cycloalkenyl radical with up to 11 carbon atoms; and their pharmaceutically acceptable salts.

13. Sodium D-α-(4-cyclopropanecarbonylamino-benzoylamino)-benzylpenicillin.

14. Sodium D-α-(4-cyclopentanecarbonylamino-2-hydroxy-benzoylamino)-benzylpenicillin.

15. Sodium D-α-(4-cyclopentanecarbonylamino-benzoylamino)-benzylpenicillin.

16. Sodium D-α-(4-cycloheptanecarbonylamino-benzoylamino)-benzylpenicillin.

17. Sodium D-α-[4-(4-cycloheptene-1-carbonylamino-benzoylamino)]-benzylpenicillin.

18. Sodium D-α-[4(3,4,5-trimethoxybenzoylamino-benzoylamino)]-benzylpenicillin.

19. Sodium D-α-[4(4-aminobenzoylamino-benzoylamino)]-benzylpenicillin.

20. Sodium D-α-(4-formylamino-benzoylamino)-benzylpenicillin.

21. Sodium D-α-[4-(3,4,5-trimethoxybenzoylamino-cinnamoylamino)]-benzylpenicillin.

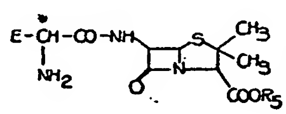
22. Sodium D-α-[4-(p-methylsulphonylbenzoyl-amino-benzoylamino)]-benzylpenicillin.

23. Sodium D-α-[4-cyclopentanecarbonyl-amino-benzoylamino]-(p-hydroxybenzoyl)-penicillin.

24. Compounds according to claim 1 that are hereinbefore expressly mentioned in any of Examples 1 to 79 but not claimed in any of claim 13 to 20.

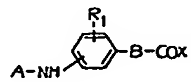
25. Compounds according to claim 1 that are hereinbefore expressly mentioned in Examples 80 and 81.

26. A process for the production of a compound according to any of claims 1 to 20 in which an ampicillin derivative of the general formula:—



(II)

is reacted with a compound of the general formula:—



(III)

in which general formulae

R_1, A, B and E are as defined in any of claims 1 to 12;

R_5 is a hydrogen, trimethylammonium or sodium atom or molecule; and

X is a labile radical at a temperature of −20° to +50°C in a diluent and in the presence of a base.

27. A process according to claim 26 in which the reaction is carried out at −15 to +20°C.

28. A process according to claim 26 or 27 in which the base is a tertiary organic base.

29. A process according to claim 26, 27 or 28 in which X is an acyloxy or halogen or activated ester radical.

30. A process according to claim 26 in which X is an acyloxy or activated ester radical and the penicillin of general formula II is used in a molar excess of 10 to 30%.

31. A process according to claim 26 in which X is a halogenation and the compound of general formula II is used in a molar excess of 10 to 20%.

32. A process according to any of claims 26 to 31 wherein the compound of general formula III in which X is a labile radical is produced by reacting an acylated aromatic amino carboxylic acid of the general formula III in which X is a hydroxyl radical at the carboxyl group with a compound containing the labile radical in an anhydrous organic solvent in the presence of about 1 molar equivalent of a tertiary organic base at −60 to +30°C; in which process the compound of general formula III in which X is a labile radical is not isolated before reaction with the ampicillin derivative of general formula II.

33. A process for the production of compounds according to claim 1 substantially as hereinbefore described in any of Examples 1 to 79.

34. A process for the production of compounds according to claim 1 substantially as hereinbefore described in Example 80 or 81.

35. Compounds according to claim 1 whenever produced by a process according to any of claims 26 to 33.

36. Compounds according to claim 1 whenever produced by a process according to claim 34.

37. A pharmaceutical composition containing as an active ingredient a compound according to any of claims 1 to 20 and 35 in admixture with a solid or liquefied gaseous diluent or in admixture with a liquid diluent other than a solvent of molecular weight less than 200 except in the presence of a surface-active agent.

38. A pharmaceutical composition containing as an active ingredient a compound according to any of claims 1 to 20 and 35 in the form of a sterile or isotonic aqueous solution.

39. A pharmaceutical composition according to claim 37 or 38 containing 0.5 to 95% of the said active ingredient by weight.

40. A pharmaceutical composition according to claim 37, 38 or 39 in which the said active compound is according to any of claims 21—23 and 36.

41. A pharmaceutical composition according to claim 37 or 38 substantially as hereinbefore described.

42. A medicament in dosage unit form comprising a compound according to any of claims 1 to 20 and 35 either alone or in admixture with a diluent.

43. A medicament in the form of tablets, pills, dragees, capsules, ampoules or suppositories comprising a compound according to any of claims 1 to 20 and 35 either alone or in admixture with a diluent.

44. A medicament according to claims 42 or 43 in which the said active compound is a compound according to any of claims 21—23 and 36.

45. A medicament in dosage unit form substantially as hereinbefore described.

46. A method of combating bacterial infections in non-human animals, and of promoting the growth of animals, comprising administering to the animals an active compound according to any of claims 1 to 20 and 35 either alone or in admixture with a diluent or in the form of a medicament according to claim 43 or mixed with fodder.

47. A method according to claim 46 for combating bacterial infections in which the said active compound is administered perorally or parentorally.

48. A method according to claim 46 or 47 in which the said active compound is a compound according to any of claims 21—23 and 36.

49. A method according to claim 46 substantially as hereinbefore described.

50. Medicated fodder comprising an animal feedstuff and a compound according to any of claims 1 to 20 and 35.

51. Medicated fodder comprising an animal feedstuff and a compound according to any of claims 21—23 and 36.

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